PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C07D 413/06, 401/06, 403/06, 471/04, 413/14, 495/04, C07F 7/18, A61K 31/535, 31/495, A61P 29/00, 3/00, 27/02 // (C07D 413/06, 265:00, 241:00)

A1

(11) International Publication Number: **WO 00/35915**

(43) International Publication Date: 22 June 2000 (22.06.00)

(21) International Application Number: PCT/JP99/06943

(22) International Filing Date: 10 December 1999 (10.12.99)

(30) Priority Data:

PP 7706	14 December 1998 (14.12.98)	AU
PQ 3568	21 October 1999 (21.10.99)	AU

(71) Applicant *(for all designated States except US)*: FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: TAKE, Kazuhiko [JP/JP]; 3-3-2-201, Kouyoudai, Tondabayashi-shi, Osaka 584-0082 (JP). KONISHI, Nobukiyo [JP/JP]; 22-7, Aotanai, Nagaokakyo-shi, Kyoto 617-0811 (JP). SHIGENAGA, Shinji [JP/JP]; 7-3-75-103, Yokoo, Suma-ku, Kobe-shi, Hyogo 654-0131 (JP). KAYAKIRI, Natsuko [JP/JP]; 7-11, Aobaokaminami, Suita-shi, Osaka 565-0802 (JP). AZAMI, Hidenori [JP/JP]; 3-5-2-1105, Sumiregaoka, Takarazuka-shi, Hyogo 665-0847 (JP). EIKYU, Yoshiteru [JP/JP]; 559-1-303, Hourencho, Nara-shi, Nara 630-8113 (JP). NAKAI, Kazuo [JP/JP]; 1-27-18-503, Mukonosohigashi, Amagasaki-shi, Hyogo 661-0032 (JP). ISHIDA, Junya [JP/JP]; 4-20-608, Kumano-cho, Nishinomiya-shi, Hyogo 663-8103 (JP). MORITA, Masataka [JP/JP]; 2-2-10-A103, Midorigaoka, Ikeda-shi, Osaka 563-0026 (JP).

(74) Agent: TABUSHI, Eiji; Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaki-shi, Osaka 532-8514 (JP).

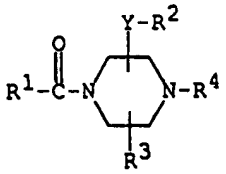
(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PIPERAZINE DERIVATIVES



(I)

(57) Abstract

This invention relates to piperazine derivatives of formula (I) wherein each symbol is as defined in the description, and its pharmaceutically acceptable salt, to processes for preparation thereof, to pharmaceutical composition comprising the same, and to a use of the same for treating or preventing Tachykinin-mediated diseases in human being or animals.

D E S C R I P T I O N

PIPERAZINE DERIVATIVES

TECHNICAL FIELD

The present invention relates to new piperazine derivatives and a salt thereof.

More particularly, it relates to new piperazine derivatives and a salt thereof which have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism, Neurokinin B antagonism, and the like, to a process for preparation thereof, to a pharmaceutical composition comprising the same, and to a use of the same as a medicament.

Accordingly, one object of the present invention is to provide new and useful piperazine derivatives and a salt thereof which have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism, Neurokinin B antagonism, and the like.

Another object of the present invention is to provide a process for the preparation of said piperazine derivatives and a salt thereof.

A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said piperazine derivatives and a pharmaceutically acceptable salt thereof.

Still further object of the present invention is to provide a use of said piperazine derivatives or a pharmaceutically acceptable salt thereof as Tachykinin antagonist, especially Substance P antagonist, Neurokinin A antagonist or Neurokinin B antagonist, useful for treating or preventing Tachykinin-mediated diseases, for example, respiratory diseases such as asthma, bronchitis, rhinitis, couph, expectoration, and the like; ophthalmic diseases such

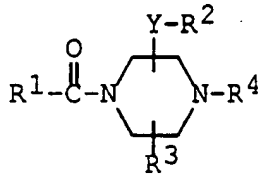
as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis, and the like; inflammatory diseases such as rheumatoid arthritis, osteoarthritis, and the like; pains or aches (e.g., migraine, headache, toothache, cancerous pain, back pain, etc.); and the like in human being or animals.

BACKGROUND ART

Some piperazine derivatives having pharmaceutical activities such as Tachykinin antagonism have been known as described in WO 97/22597 A1 and WO 98/57954 A1.

DISCLOSURE OF INVENTION

The object compound of the present invention can be represented by the following general formula (I):



(I)

wherein

Y is bond or lower alkylene,

R^1 is aryl which is substituted with 1 to 3 same or different substituent(s) selected from the group consisting of halogen, lower alkyl, lower alkoxy, mono(or di or tri)halo(lower)alkyl, nitro, amino, lower alkylamino, di(lower)alkylamino, lower alkylthio, lower alkylsulfonyl, cyclo(lower)alkylsulfonyl, aminosulfonyl, lower alkylaminosulfonyl, di(lower)alkylaminosulfonyl, pyrrolidinylsulfonyl, morpholinylsulfonyl, pyrrolylsulfonyl, pyridylsulfonyl, pyrrolyl and pyridyl;

R^2 is aryl which is substituted with 1 to 3 same or different

substituent(s) selected from the group consisting of lower alkyl, mono(or di or tri)halo(lower)alkyl, mono(or di or tri)halo(lower)alkylsulfonyloxy, halogen, lower alkylenedioxy, lower alkoxy, lower alkoxycarbonyl, lower alkoxy(lower)alkoxy(lower)alkoxy, hydroxy, diphenyl(lower)alkylsilyloxy, tri(lower)alkylsilyloxy, hydroxy(lower)alkyl, cyano, amino, [mono(or di or tri)halo(lower)alkylcarbonyl]amino, lower alkylamino, N-(lower alkyl)-[mono(or di or tri)halo(lower)alkylcarbonyl]amino, pyrrolidinyl and morpholinyl which may be substituted with lower alkoxy(lower)alkyl or lower alkyl;

R^3 is hydrogen or lower alkyl; and

R^4 is (3-pyridyl)methyl;

(3-pyridyl)ethyl;

3-(3-pyridyl)propyl;

3-(3-pyridyl)propenyl;

3-(3-pyridyl)propynyl;

thiazolyl(lower)alkyl, 1,2,4-thiadiazolyl(lower)alkyl or 1,2,4-oxadiazolyl(lower)alkyl, each of which is substituted with halogen, amino, lower alkylamino or di(lower)alkylamino;

pyrazolylmethyl which may be substituted with triphenyl(lower)alkyl or hydroxy(lower)alkyl;

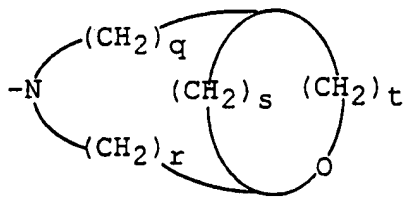
pyrazolyl(lower)alkyl which is substituted with lower alkyl, lower alkoxy(lower)alkylmorpholinyl(lower)alkyl or lower alkoxy(lower)alkylmorpholinylcarbonyl(lower)-alkyl;

pyrrolidinyl(lower)alkyl which is substituted with 1 or 2 same or different substituent(s) selected from the group consisiting of hydroxy, hydroxy(lower)alkyl, lower alkoxy and lower alkoxy(lower)alkyl;

piperidylmethyl;

piperidyl(lower)alkyl which is substituted with 1 or 2 same or different substituent(s) selected from the group

consisting of halogen, lower alkyl and lower alkoxy-(lower)alkyl;
[2,6-di[hydroxy(lower)alkyl]piperidyl](lower)alkyl;
(2,6-dimethylmorpholino)(lower)alkyl;
(2,2-dimethylmorpholino)(lower)alkyl;
(3,3-dimethylmorpholino)(lower)alkyl;
(cis-3,5-dimethylmorpholino)(lower)alkyl;
((3S,5S)-3,5-dimethylmorpholino)(lower)alkyl;
((3S,5R)-3,5-dimethylmorpholino)(lower)alkyl;
(2-methoxymethylmorpholino)(lower)alkyl;
(3-methoxymethylmorpholino)(lower)alkyl;
(2-methoxymethyl-5-methylmorpholino)(lower)alkyl;
(2-methoxymethyl-5,5-dimethylmorpholino)(lower)alkyl;
(3,5-dimethoxymethylmorpholino)(lower)alkyl;
(2,2-dimethoxymethylmorpholino)(lower)alkyl;
(2,3-dimethoxymethylmorpholino)(lower)alkyl;
(2,6-dimethoxymethylmorpholino)(lower)alkyl;
(2-methoxymethylmorpholino)(lower)alkenyl;
(3,3-dimethylmorpholino)(lower)alkynyl;
(2-methoxymethylmorpholino)(lower)alkynyl;
(2-methoxymethyl-5-methylmorpholino)(lower)alkynyl;
quinoly(lower)alkyl;
[1H-pyrrolo[3,2-b]pyridinyl](lower)alkyl;
[4,5,6,7-tetrahydrothieno[3,2-c]pyridinyl](lower)alkyl;
[3,4-dihydro-2H-pyrido[3,2-b]-1,4-oxazinyl](lower)alkyl;
(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)(lower)-alkyl; or
lower alkyl which is substituted with a saturated heterocyclic group of the formula :



(wherein
r, s and t are each integer of 1 to 2, and

q is integer of 0 to 2)

which may be substituted with one or two lower alkyl,

provided that when

R^4 is 3-(3-pyridyl)propyl;

3-(3-pyridyl)propenyl;

pyrazolylmethyl which may be substituted with hydroxy(lower)alkyl;

(2-methoxymethylmorpholino)(lower)alkyl;

(3-methoxymethylmorpholino)(lower)alkyl; or

(2-methoxymethylmorpholino)(lower)alkynyl, then

R^2 is not di(lower)alkylphenyl.

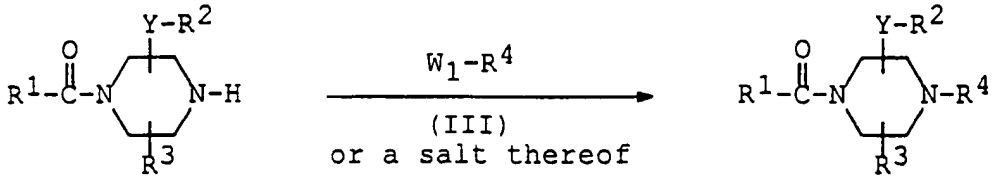
It is to be noted that the object compound (I) may include one or more stereoisomers due to asymmetric carbon atom(s) and double bond, and all of such isomers and a mixture thereof are included within the scope of the present invention.

It is further to be noted that isomerization or rearrangement of the object compound (I) may occur due to the effect of the light, acid, base or the like, and the compound obtained as the result of said isomerization or rearrangement is also included within the scope of the present invention.

It is also to be noted that the solvating form of the compound (I) (e.g. hydrate, etc.) and any form of the crystal of the compound (I) are included within the scope of the present invention.

According to the present invention, the object compound (I) or a salt thereof can be prepared by processes which are illustrated in the following schemes.

Process 1

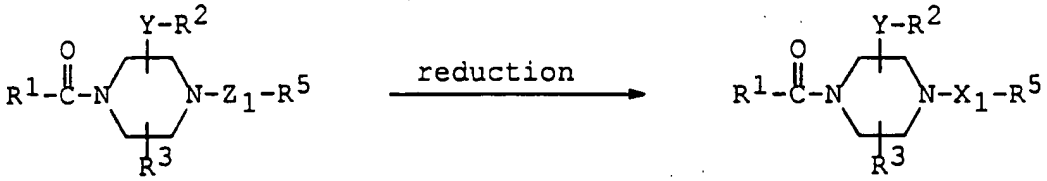


(II)
or its reactive derivative at the imino group or a salt thereof

(III)
or a salt thereof

(I)
or a salt thereof

Process 2



(Ia)
or a salt thereof

(Ib)
or a salt thereof

wherein
Y, R^1, R^2, R^3 and R^4 are each as defined above,
X_1 is lower alkylene,
Z_1 is lower alkynylene,
R^5 is 3-pyridyl, and
W_1 is a leaving group.

As to the starting compounds (II) and (III), some of them are novel and can be prepared by the procedures described in the Preparations and Examples mentioned later or similar manners thereto.

Suitable salts of the starting and object compounds are conventional non-toxic and pharmaceutically acceptable salt and include an acid addition salt such as an organic acid salt (e.g. acetate, trifluoroacetate, fumarate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate,

toluenesulfonate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate, phosphate, etc.), or a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), or a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), or the like.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention intends to include within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise indicated.

Suitable "lower alkylene" may include straight or branched one having 1 to 6, preferably 1 to 4, carbon atom(s), such as methylene, ethylene, trimethylene, propylene, tetramethylene, methylmethylene, methyltrimethylene, hexamethylene, and the like, in which the preferred one is methylene, ethylene, trimethylene or methylmethylene.

Suitable "lower alkynylene" may include one having 2 to 6 carbon atoms, such as ethynylene, propynylene, butynylene, and the like, in which the preferred one is propynylene or butynylene.

Suitable "halogen" and "halogen" moiety in the terms "mono(or di or tri)halo(lower)alkyl", "mono(or di or tri)halo(C_1-C_4)alkyl", etc. may include fluorine, chlorine, bromine and iodine.

Suitable "lower alkyl" and "lower alkyl" moiety in the

terms "hydroxy(lower)alkyl", "pyrazolyl(lower)alkyl", etc. may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl and the like, in which the preferred one is C_1-C_4 alkyl and the most preferred one is methyl, ethyl or propyl.

Suitable "lower alkenyl" moiety in the term "(2-methoxymethylmorpholino)(lower)alkenyl" may include vinyl, 1-(or 2-)propenyl, 1-(or 2- or 3-)butenyl, 1-(or 2- or 3- or 4-)pentenyl, 1-(or 2- or 3- or 4- or 5-)hexenyl, methylvinyl ethylvinyl, 1-(or 2- or 3-)methyl-1-(or 2-)propenyl, 1-(or 2- or 3-)ethyl-1-(or 2-)propenyl, 1-(or 2- or 3- or 4-)methyl-1-(or 2- or 3-)butenyl, and the like, in which more preferable example may be C_2-C_4 alkenyl.

Suitable "aryl" may include phenyl, naphthyl, and the like, in which the preferred one is C_6-C_{10} aryl and the most preferred one is phenyl or naphthyl.

Suitable "lower alkoxy" and "lower alkoxy" moiety in the terms "lower alkoxy(lower)alkylmorpholinyl(lower)alkyl", "lower alkoxy(lower)alkylmorpholinylcarbonyl(lower)alkyl", etc. may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentyloxy, t-pentyloxy, hexyloxy and the like, in which the preferred one is C_1-C_4 alkoxy and the most preferred one is methoxy.

Suitable "leaving group" may include lower alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentoxy, etc.), aryloxy (e.g., phenoxy, naphthoxy, etc.), an acid residue or the like.

Suitable "acid residue" may be halogen (e.g., chlorine, bromine, iodine, etc.), sulfonyloxy (e.g., methanesulfonyloxy, phenylsulfonyloxy, mesitylenesulfonyloxy, toluenesulfonyloxy, etc.) or the like.

Preferred embodiments of the object compound (I) are as follows:

Y is lower alkylene (more preferably C_1-C_4 alkylene, most preferably methylene);

R^1 is phenyl which is substituted with 1 or 2 same or different substituent(s) selected from the group consisting of halogen (more preferably fluorine or chlorine), lower alkyl (more preferably C_1-C_4 alkyl, most preferably methyl), lower alkoxy (more preferably C_1-C_4 alkoxy, most preferably methoxy), mono(or di or tri)halo(lower)alkyl (more preferably trihalo(lower)alkyl, most preferably trifluoromethyl), nitro, amino, lower alkylamino (more preferably C_1-C_4 alkylamino, most preferably methylamino), di(lower)alkylamino (more preferably di(C_1-C_4)alkylamino, most preferably dimethylamino), lower alkylthio (more preferably C_1-C_4 alkylthio, most preferably methylthio), lower alkylsulfonyl (more preferably C_1-C_4 alkylsulfonyl, most preferably methanesulfonyl), cyclo(lower)alkylsulfonyl (more preferably cyclo(C_1-C_6)alkylsulfonyl, most preferably cyclopentylsulfonyl), aminosulfonyl, lower alkylamino-sulfonyl (more preferably C_1-C_4 alkylaminosulfonyl, most preferably methylaminosulfonyl), di(lower)alkylamino-sulfonyl (more preferably di(C_1-C_4)alkylaminosulfonyl, most preferably dimethylaminosulfonyl), pyrrolidinylsulfonyl (more preferably pyrrolidinosulfonyl), morpholinylsulfonyl (more preferably morpholinosulfonyl), pyrrolylsulfonyl (more preferably 1-pyrrolylsulfonyl), pyridylsulfonyl (more preferably 4-pyridylsulfonyl), pyrrolyl (more preferably 1-pyrrolyl) and pyridyl (more preferably 4-pyridyl);

R^2 is phenyl which is substituted with 1 or 2 same or different substituent(s) selected from the group consisting of lower alkyl (more preferably C_1-C_4 alkyl, most preferably methyl or isopropyl), mono(or di or tri)halo(lower)alkyl (more preferably mono(or di or

tri)halo(C_1-C_4)alkyl, most preferably trifluoromethyl), mono(or di or tri)halo(lower)alkylsulfonyloxy (more preferably mono(or di or tri)halo(C_1-C_4)alkylsulfonyl, most preferably trifluoromethylsulfonyloxy), halogen (more preferably chlorine or fluoride), lower alkylenedioxy (more preferably C_1-C_4 alkylenedioxy, most preferably methylenedioxy or ethylenedioxy), lower alkoxy (more preferably C_1-C_4 alkoxy, most preferably methoxy), lower alkoxycarbonyl (more preferably C_1-C_4 alkoxycarbonyl, most preferably methoxycarbonyl), lower alkoxy(lower)alkoxy(lower)alkoxy (more preferably C_1-C_4 alkoxy(C_1-C_4)alkoxy(C_1-C_4)alkoxy, most preferably (2-methoxyethoxy)methoxy), hydroxy, diphenyl(lower)alkylsilyloxy (more preferably diphenyl(C_1-C_4)alkylsilyloxy, most preferably diphenyl(tert-butyl)silyloxy), tri(lower)alkylsilyloxy (more preferably tri(C_1-C_4)alkylsilyloxy, most preferably dimethyl(tert-butyl)silyloxy), hydroxy(lower)alkyl (more preferably hydroxy(C_1-C_4)alkyl, most preferably hydroxymethyl or 1-hydroxy-1-methylethyl), cyano, amino, [mono(or di or tri)halo(lower)alkylcarbonyl]amino (more preferably [mono(or di or tri)halo(C_1-C_4)alkylcarbonyl]amino, most preferably (trifluoromethylcarbonyl)amino), lower alkylamino (more preferably C_1-C_4 alkylamino, methylamino), N-(lower alkyl)-[mono(or di or tri)halo(lower)alkylcarbonyl]amino (more preferably N-(C_1-C_4 alkyl)-[mono(or di or tri)halo(C_1-C_4)alkylcarbonyl]amino, most preferably N-methyl-(trifluoromethylcarbonyl)amino), pyrrolidinyl (more preferably pyrrolidino) and morpholinyl (more preferably morpholino) which may be substituted with lower alkoxy(lower)alkyl (more preferably C_1-C_4 alkoxy(C_1-C_4)alkyl, most preferably methoxymethyl) or lower alkyl (more preferably C_1-C_4 alkyl, most preferably methyl);

R^3 is hydrogen; and

R^4 is (3-pyridyl)methyl;

(3-pyridyl)ethyl (more preferably 2-(3-pyridyl)ethyl);

3-(3-pyridyl)propyl;

3-(3-pyridyl)propenyl (more preferably 3-(3-pyridyl)-2-propenyl);

3-(3-pyridyl)propynyl (more preferably 3-(3-pyridyl)-2-propynyl);

thiazolyl(lower)alkyl (more preferably thiazolyl(C_1-C_4)alkyl, most preferably 4-thiazolymethyl), 1,2,4-thiadiazolyl(lower)alkyl (more preferably 1,2,4-thiadiazolyl(C_1-C_4)alkyl, most preferably 1,2,4-thiadiazolyl-3-ylmethyl) or 1,2,4-oxadiazolyl(lower)-alkyl (more preferably 1,2,4-oxadiazolyl(C_1-C_4)alkyl, most preferably 1,2,4-oxadiazolyl-5-ylmethyl), each of which is substituted with halogen (more preferably bromine), amino, lower alkylamino (more preferably C_1-C_4 alkylamino, most preferably methylamino) or di(lower)alkylamino (more preferably di(C_1-C_4)alkylamino, most preferably dimethylamino);

pyrazolylmethyl (more preferably (4-pyrazolyl)methyl or (5-pyrazolyl)methyl) which may be substituted with triphenyl(lower)alkyl (more preferably triphenyl(C_1-C_4)alkyl, most preferably triphenylmethyl) or hydroxy(lower)alkyl (more preferably hydroxy(C_1-C_4)-alkyl, most preferably 2-hydroxyethyl);

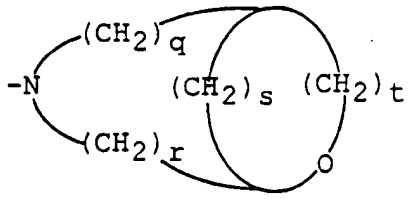
pyrazolyl(lower)alkyl (more preferably pyrazolyl-(C_1-C_4)alkyl, most preferably (4-pyrazolyl)methyl, (5-pyrazolyl)methyl or 3-(4-pyrazolyl)propyl) which is substituted with lower alkyl (more preferably C_1-C_4 alkyl, most preferably methyl), (lower)alkoxy(lower)-alkylmorpholinyl(lower)alkyl (more preferably (C_1-C_4)-alkoxy(C_1-C_4)alkylmorpholinyl(C_1-C_4)alkyl, most preferably 2-(2-methoxymethylmorpholino)ethyl) or (lower)alkoxy(lower)alkylmorpholinylcarbonyl(lower)alkyl

(more preferably (C_1-C_4)alkoxy(C_1-C_4)-alkylmorpholinylcarbonyl(C_1-C_4)alkyl, most preferably (2-methoxymethylmorpholino)carbonylmethyl); pyrrolidinyl(lower)alkyl (more preferably pyrrolidinyl(C_1-C_4)alkyl, most preferably 2-pyrrolidinoethyl) which is substituted with 1 or 2 same or different substituent(s) selected from the group consisiting of hydroxy, hydroxy(lower)alkyl (more preferably hydroxy(C_1-C_4)alkyl, most preferably hydroxymethyl), lower alkoxy (more preferably C_1-C_4 alkoxy, most preferably methoxy) and lower alkoxy(lower)alkyl (more preferably C_1-C_4 alkoxy(C_1-C_4)alkyl, most preferably methoxymethyl); piperidylmethyl (more preferably (4-piperidyl)methyl); piperidyl(lower)alkyl (more preferably piperidyl(C_1-C_4)-alkyl, most preferably 2-piperidinoethyl) which is substituted with 1 or 2 same or different substituent(s) selected from the group of halogen (more preferably fluorine), lower alkyl (more preferably C_1-C_4 alkyl, most preferably methyl) and lower alkoxy(lower)alkyl (more preferably C_1-C_4 alkoxy(C_1-C_4)alkyl, most preferably methoxymethyl); [2,6-di[hydroxy(lower)alkyl]piperidyl](lower)alkyl (more preferably [2,6-di[hydroxy(C_1-C_4)alkyl]piperidyl](C_1-C_4)alkyl, most preferably 2-[2,6-di(hydroxymethyl)piperidino]ethyl); (2,6-dimethylmorpholino)(lower)alkyl (more preferably (2,6-dimethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(2,6-dimethylmorpholino)ethyl); (2,2-dimethylmorpholino)(lower)alkyl (more preferably (2,2-dimethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(2,2-dimethylmorpholino)ethyl); (3,3-dimethylmorpholino)(lower)alkyl (more preferably (3,3-dimethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(3,3-dimethylmorpholino)ethyl);

(cis-3,5-dimethylmorpholino)(lower)alkyl (more preferably (cis-3,5-dimethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(cis-3,5-dimethylmorpholino)ethyl);
((3S,5S)-3,5-dimethylmorpholino)(lower)alkyl (more preferably ((3S,5S)-3,5-dimethylmorpholino)(C_1-C_4)alkyl, most preferably 2-((3S,5S)-3,5-dimethylmorpholino)-ethyl);
((3S,5R)-3,5-dimethylmorpholino)(lower)alkyl (more preferably ((3S,5R)-3,5-dimethylmorpholino)(C_1-C_4)alkyl, most preferably 2-((3S,5R)-3,5-dimethylmorpholino)-ethyl);
(2-methoxymethylmorpholino)(lower)alkyl (more preferably (2-methoxymethylmorpholino)(C_1-C_4)alkyl, most preferably 3-(2-methoxymethylmorpholino)propyl or 2-(2-methoxymethylmorpholino)ethyl);
(3-methoxymethylmorpholino)(lower)alkyl (more preferably (3-methoxymethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(3-methoxymethylmorpholino)ethyl);
(2-methoxymethyl-5-methylmorpholino)(lower)alkyl (more preferably (2-methoxymethyl-5-methylmorpholino)-(C_1-C_4)alkyl, most preferably 2-(2-methoxymethyl-5-methylmorpholino)ethyl);
(2-methoxymethyl-5,5-dimethylmorpholino)(lower)alkyl (more preferably (2-methoxymethyl-5,5-dimethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(2-methoxymethyl-5,5-dimethylmorpholino)ethyl);
(3,5-dimethoxymethylmorpholino)(lower)alkyl (more preferably (3,5-dimethoxymethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(3,5-dimethoxymethylmorpholino)ethyl);
(2,2-dimethoxymethylmorpholino)(lower)alkyl (more preferably (2,2-dimethoxymethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(2,2-dimethoxymethylmorpholino)ethyl);
(2,3-dimethoxymethylmorpholino)(lower)alkyl (more preferably (2,3-dimethoxymethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(2,3-dimethoxymethylmorpholino)ethyl);

(2,6-dimethoxymethylmorpholino)(lower)alkyl (more preferably (2,6-dimethoxymethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(2,6-dimethoxymethylmorpholino)ethyl);
(2-methoxymethylmorpholino)(lower)alkenyl (more preferably (2-methoxymethylmorpholino)(C_2-C_4)alkenyl, most preferably 4-(2-methoxymethylmorpholino)-2-butenyl);
(3,3-dimethylmorpholino)(lower)alkynyl (more preferably (3,3-dimethylmorpholino)(C_2-C_4)alkynyl, most preferably 4-(3,3-dimethylmorpholino)-2-butynyl);
(2-methoxymethylmorpholino)(lower)alkynyl (more preferably (2-methoxymethylmorpholino)(C_2-C_4)alkynyl, most preferably 4-(2-methoxymethylmorpholino)-2-butynyl);
(2-methoxymethyl-5-methylmorpholino)(lower)alkynyl (more preferably (2-methoxymethyl-5-methylmorpholino)(C_2-C_4)alkynyl, most preferably 4-(2-methoxymethyl-5-methylmorpholino)-2-butynyl);
quinolyl(lower)alkyl (more preferably quinolyl(C_1-C_4)alkyl, most preferably (6-quinolyl)methyl);
[1H-pyrrolo[3,2-b]pyridinyl](lower)alkyl (more preferably [1H-pyrrolo[3,2-b]pyridinyl](C_1-C_4)alkyl, most preferably [1H-pyrrolo[3,2-b]pyridin-3-yl]methyl);
[4,5,6,7-tetrahydrothieno[3,2-c]pyridinyl](lower)alkyl (more preferably [4,5,6,7-tetrahydrothieno[3,2-c]-pyridinyl](C_1-C_4)alkyl, most preferably 2-[4,5,6,7-tetrahydrothieno[3,2-c]pyridin-5-yl]ethyl);
[3,4-dihydro-2H-pyrido[3,2-b]-1,4-oxazinyl](lower)alkyl (more preferably [3,4-dihydro-2H-pyrido[3,2-b]-1,4-oxazinyl](C_1-C_4)alkyl, most preferably 2-[3,4-dihydro-2H-pyrido[3,2-b]-1,4-oxazin-4-yl]ethyl);
(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)(lower)alkyl (more preferably (5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)(C_1-C_4)alkyl, most preferably 2-(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)ethyl); or

lower alkyl (more preferably C_1-C_4 alkyl, most preferably ethyl) which is substituted with a saturated heterocyclic group of the formula:



(wherein
r, s and t are each integer of 1 to 2, and
q is integer of 0 to 2)

(more preferably (1S,4S)-2-aza-5-oxabicyclo[2.2.1]-heptan-2-yl) which may be substituted with one or two lower alkyl (more preferably C_1-C_4 alkyl, most preferably methyl)).

More preferred embodiments of the object compound (I) are as follows:

Y is lower alkylene (more preferably C_1-C_4 alkylene, most preferably methylene);

R^1 is phenyl which is substituted with 1 or 2 same or different substituent(s) selected from the group consisting of halogen, lower alkyl, lower alkoxy, mono(or di or tri)halo(lower)alkyl, nitro, amino, lower alkylamino, di(lower)alkylamino, lower alkylthio, lower alkylsulfonyl, cyclo(lower)alkylsulfonyl, aminosulfonyl, lower alkylaminosulfonyl, di(lower alkyl)aminosulfonyl, pyrrolidinylsulfonyl, morpholinylsulfonyl, pyrrolylsulfonyl, pyridylsulfonyl, pyrrolyl and pyridyl [more preferably dihalophenyl, bis(trihalo(lower)alkyl)phenyl, (trihalo(lower)alkyl)(halo)phenyl, (trihalo(lower)alkyl)((lower)alkyl)phenyl, (trihalo(lower)alkyl)((lower)alkoxy)phenyl, (trihalo(lower)alkyl)(nitro)phenyl, (trihalo(lower)alkyl)(lower alkylamino)phenyl,

(trihalo(lower)alkyl)(di(lower)alkylamino)phenyl, (trihalo(lower)alkyl)((lower)alkylthio)phenyl, (trihalo(lower)alkyl)((lower)alkylsulfonyl)phenyl, (trihalo(lower)alkyl)(cyclo(lower)alkylsulfonyl)phenyl, (trihalo(lower)alkyl)(aminosulfonyl)phenyl, (trihalo(lower)alkyl)(lower alkylaminosulfonyl)phenyl, (trihalo(lower)alkyl)(di(lower)alkylaminosulfonyl)-phenyl, (trihalo(lower)alkyl)(pyrrolidinylsulfonyl)-phenyl, (trihalo(lower)alkyl)(morpholinylsufonyl)phenyl, (trihalo(lower)alkyl)(pyridylsulfonyl)phenyl, (trihalo(lower)alkyl)(pyrrolyl)phenyl or (trihalo(lower)alkyl)(pyridyl)phenyl, most preferably 3,5-dichlorophenyl, 3,5-bis(trifluoromethyl)phenyl, 3-fluoro-5-trifluoromethylphenyl, 3-chloro-5-trifluoromethylphenyl, 3-methyl-5-trifluoromethylphenyl, 3-methoxy-5-trifluoromethylphenyl, 3-nitro-5-trifluoromethylphenyl, 3-methylamino-5-trifluoromethylphenyl, 3-dimethylamino-5-trifluoromethylphenyl, 3-methylthio-5-trifluoromethylphenyl, 3-methanesulfonyl-5-trifluoromethylphenyl, 3-cyclopentylsulfonyl-5-trifluoromethylphenyl, 3-aminosulfonyl-5-trifluoromethylphenyl, 3-methylaminosulfonyl-5-trifluoromethylphenyl, 3-dimethylaminosulfonyl-5-trifluoromethylphenyl, 3-pyrrolidinosulfonyl-5-trifluoromethylphenyl, 3-morpholinosulfonyl-5-trifluoromethylphenyl, 3-(4-pyridyl)sulfonyl-5-trifluoromethylphenyl, 3-(1-pyrrolyl)-5-trifluoromethylphenyl or 3-(4-pyridyl)-5-trifluoromethylphenyl];

R^2 is phenyl which is substituted with 1 or 2 same or different substituent(s) selected from the group consisting of lower alkyl, mono(or di or tri)halo(lower)alkyl, mono(or di or tri)halo(lower)alkylsulfonyloxy, halogen, lower

alkylenedioxy, lower alkoxy, lower alkoxycarbonyl, lower alkoxy(lower)alkoxy(lower)alkoxy, hydroxy, diphenyl(lower)alkylsilyloxy, tri(lower)alkylsilyloxy, hydroxy(lower)alkyl, cyano, amino, [mono(or di or tri)halo(lower)alkylcarbonyl]amino, lower alkylamino, N-(lower alkyl)-[mono(or di or tri)halo(lower)alkylcarbonyl]amino, pyrrolidinyl and morpholinyl which may be substituted with lower alkoxy(lower)alkyl or lower alkyl [more preferably ((lower)alkylenedioxy)phenyl, (lower alkoxy)phenyl, halophenyl, dihalophenyl, (trihalo(lower)alkyl)phenyl, (trihalo(lower)alkyl)(lower alkyl)phenyl, (halo)(lower alkyl)phenyl, (halo)(lower alkoxy)phenyl, (halo)(hydroxy)phenyl, (halo)(diphenyl(lower)alkylsilyloxy)phenyl, (trihalo(lower)alkyl)(hydroxy)-phenyl, (hydroxy(lower)alkyl)(hydroxy)phenyl, (cyano)(hydroxy)phenyl, (dihalo(lower)alkyl)(hydroxy)-phenyl, (lower alkyl)(amino)phenyl, (lower alkyl)(lower alkylamino)phenyl, (lower alkyl)(mono(or di or tri)halo(lower)alkylsulfonyloxy)phenyl, (lower alkyl)[[mono(or di or tri)halo(lower)alkylcarbonyl]-amino]phenyl, (lower alkyl)[N-(lower alkyl)-[mono(or di or tri)halo(lower)alkylcarbonyl]amino]phenyl, (lower alkyl)(diphenyl(lower)alkylsilyloxy)phenyl, (lower alkyl)(lower alkoxy(lower)alkoxy(lower)alkoxy)phenyl, (lower alkyl)(tri(lower)alkylsilyloxy)phenyl, (lower alkoxycarbonyl)(tri(lower)alkylsilyloxy)phenyl, (hydroxy(lower)alkyl)(tri(lower)alkylsilyloxy)phenyl, (lower alkyl)(hydroxy)phenyl, (lower alkyl)(pyrrolidinyl)phenyl, (lower alkyl)(morpholinyl)phenyl, (lower alkyl)(lower alkoxy-(lower)alkylmorpholinyl)phenyl or (lower alkyl)(lower alkyl)morpholinyl)phenyl, most preferably 1,4-benzodioxan-6-yl, 4-methoxyphenyl, 4-fluorophenyl, 4-chlorophenyl, 3,4-difluorophenyl, 4-(trifluoromethyl)-

phenyl, 3-methoxy-4-trifluoromethylphenyl, 4-fluoro-3-methylphenyl, 4-fluoro-3-methoxy-phenyl, 3-fluoro-4-methylphenyl, 4-fluoro-3-hydroxyphenyl, 4-chloro-3-methoxyphenyl, 4-chloro-3-(dimethyl(tert-butyl)silyloxy)phenyl, 4-chloro-3-hydroxy-phenyl, 3-hydroxy-4-(trifluoromethyl)phenyl, 3-hydroxy-4-(hydroxymethyl)phenyl, 3-hydroxy-4-methylphenyl, 3-hydroxy-4-(1-hydroxy-1-methylethyl)phenyl, 4-cyano-3-hydroxyphenyl, 3-hydroxy-4-(difluoromethyl)phenyl, 3-hydroxy-4-isopropylphenyl, 3-amino-4-methylphenyl, 4-methyl-3-methylaminophenyl, 4-methyl-3-(trifluoromethylsulfonyloxy)phenyl, 4-methyl-3-[(trifluoromethylcarbonyl)amino]phenyl, 4-methyl-3-[N-methyl-(trifluoromethylcarbonyl)amino]phenyl, 3-diphenyl(tert-butyl)silyloxy-4-methylphenyl, 4-methyl-3-[(2-methoxyethoxy)methoxy]phenyl, 3-dimethyl(tert-butyl)silyloxy-4-methylphenyl, 3-dimethyl(tert-butyl)silyloxy-4-methoxycarbonylphenyl, 3-dimethyl(tert-butyl)silyloxy-4-(1-hydroxy-1-methylethyl)phenyl, 4-methyl-3-pyrrolidinophenyl or 4-methyl-3-morpholinophenyl];

R^3 is hydrogen; and

R^4 is (2,6-dimethylmorpholino)(lower)alkyl (more preferably (2,6-dimethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(2,6-dimethylmorpholino)ethyl);

(2,2-dimethylmorpholino)(lower)alkyl (more preferably (2,2-dimethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(2,2-dimethylmorpholino)ethyl);

(3,3-dimethylmorpholino)(lower)alkyl (more preferably (3,3-dimethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(3,3-dimethylmorpholino)ethyl);

(cis-3,5-dimethylmorpholino)(lower)alkyl (more preferably (cis-3,5-dimethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(cis-3,5-dimethylmorpholino)ethyl);

((3S,5S)-3,5-dimethylmorpholino)(lower)alkyl (more

preferably ((3S,5S)-3,5-dimethylmorpholino)(C_1-C_4)alkyl, most preferably 2-((3S,5S)-3,5-dimethylmorpholino)-ethyl);

((3S,5R)-3,5-dimethylmorpholino)(lower)alkyl (more preferably ((3S,5R)-3,5-dimethylmorpholino)(C_1-C_4)alkyl, most preferably 2-((3S,5R)-3,5-dimethylmorpholino)-ethyl);

(2-methoxymethylmorpholino)(lower)alkyl (more preferably (2-methoxymethylmorpholino)(C_1-C_4)alkyl, most preferably 3-(2-methoxymethylmorpholino)propyl or 2-(2-methoxymethylmorpholino)ethyl);

(3-methoxymethylmorpholino)(lower)alkyl (more preferably (3-methoxymethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(3-methoxymethylmorpholino)ethyl);

(2-methoxymethyl-5-methylmorpholino)(lower)alkyl (more preferably (2-methoxymethyl-5-methylmorpholino)(C_1-C_4)-alkyl, most preferably 2-(2-methoxymethyl-5-methylmorpholino)ethyl);

(2-methoxymethyl-5,5-dimethylmorpholino)(lower)alkyl (more preferably (2-methoxymethyl-5,5-dimethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(2-methoxymethyl-5,5-dimethylmorpholino)ethyl);

(3,5-dimethoxymethylmorpholino)(lower)alkyl (more preferably (3,5-dimethoxymethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(3,5-dimethoxymethylmorpholino)ethyl);

(2,2-dimethoxymethylmorpholino)(lower)alkyl (more preferably (2,2-dimethoxymethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(2,2-dimethoxymethylmorpholino)ethyl);

(2,3-dimethoxymethylmorpholino)(lower)alkyl (more preferably (2,3-dimethoxymethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(2,3-dimethoxymethylmorpholino)ethyl);

(2,6-dimethoxymethylmorpholino)(lower)alkyl (more preferably (2,6-dimethoxymethylmorpholino)(C_1-C_4)alkyl, most preferably 2-(2,6-dimethoxymethylmorpholino)ethyl);

(2-methoxymethylmorpholino)(lower)alkenyl (more

preferably (2-methoxymethylmorpholino)(C_2-C_4)alkenyl, most preferably 4-(2-methoxymethylmorpholino)-2-butenyl);

(3,3-dimethylmorpholino)(lower)alkynyl (more preferably (3,3-dimethylmorpholino)(C_2-C_4)alkynyl, most preferably 4-(3,3-dimethylmorpholino)-2-butynyl);

(2-methoxymethylmorpholino)(lower)alkynyl (more preferably (2-methoxymethylmorpholino)(C_2-C_4)alkynyl, most preferably 4-(2-methoxymethylmorpholino)-2-butynyl); or

(2-methoxymethyl-5-methylmorpholino)(lower)alkynyl (more preferably (2-methoxymethyl-5-methylmorpholino)(C_2-C_4)alkynyl, most preferably 4-(2-methoxymethyl-5-methylmorpholino)-2-butynyl).

The Processes 1 and 2 for preparing the object compound (I) of the present invention are explained in detail in the following.

Process 1

The object compound (I) or a salt thereof can be prepared by reacting the compound (II) or its reactive derivative at the imino group or a salt thereof with the compound (III) or a salt thereof.

Suitable reactive derivative at the imino group of the compound (II) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (II) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (II) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound (II) with phosphorus trichloride or phosgene and the like.

The reaction is usually carried out in a conventional

solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvents may also be used in a mixture with water.

The reaction may also be carried out in the presence of an inorganic or organic base such as alkali metal carbonate (e.g. potassium carbonate, etc.), alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkyl-morpholine, N,N-di(lower)alkylethylamine (e.g. N,N-diisopropylethylamine, etc.), N,N-di(lower)alkylbenzylamine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

Process 2

The object compound (Ib) or a salt thereof can be prepared by subjecting the compound (Ia) or a salt thereof to a reduction reaction.

The reaction can be carried out in the manner disclosed in Example 8 mentioned later or similar manners thereto.

The object compound (I) and a pharmaceutically acceptable salt thereof have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism or Neurokinin B antagonism, and therefore are useful for treating or preventing Tachykinin-mediated diseases, particularly Substance P-mediated diseases, for example, respiratory diseases such as asthma, bronchitis (e.g. chronic bronchitis, acute bronchitis and diffuse panbronchiolitis, etc.), rhinitis, couph, expectoration, and the like;
ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like;

cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis, and the like; inflammatory diseases such as rheumatoid arthritis, osteoarthritis, and the like;

pains or aches (e.g. migraine, headache, cluster headache, toothache, cancerous pain, back pain, neuralgia, etc.); and the like.

Further, it is expected that the object compound (I) and a pharmaceutically acceptable salt thereof of the present invention are useful for treating or preventing ophthalmic diseases such as glaucoma, uveitis, and the like; gastrointestinal diseases such as ulcer, ulcerative colitis, irritable bowel syndrome, food allergy, and the like; inflammatory diseases such as nephritis, and the like; circulatory diseases such as hypertension, angina pectoris, cardiac failure, thrombosis, Raynaud's disease, and the like; epilepsy; spastic paralysis; pollakiuria; cystitis; bladder detrusor hyperreflexia; urinary incontinence; Parkinson diseases; dimentia; AIDS related dementia; Alzheimer's diseases; Down's syndrome; Huntington's chorea; carcinoid syndrome; disorders related to immune enhancement or suppression; disorders caused by Helicobacter pylori or another spiral urease-positive gram-negative bacterium; sunburn; angiogenesis or diseases caused by angiogenesis; and the like.

It is furthermore expected that the object compound (I) and a pharmaceutically acceptable salt thereof of the present invention are useful for treating or preventing chronic obstructive pulmonary diseases, particularly chronic pulmonary emphysema; iritis; proliferative vitreoretinopathy; psoriasis; inflammatory intestinal diseases, particularly Crohn's diseases; hepatitis; superficial pain on congelation, burn, herpes zoster or diabetic neuropathy; telalgia attended to hyperlipidemia; postoperative neuroma, particularly of mastectomy; vulvar vestibulitis; hemodialysis-associated

itching; lichen planus; laryngopharyngitis; bronchiectasis; coniosis; whooping cough; pulmonary tuberculosis; cystic fibrosis; emesis (e.g., nausea, retching, vomiting, acute emesis, delayed emesis, anticipatory emesis, past operative nausea and vomiting (PONV), acute and/or delayed emesis induced by drugs such as cancer chemotherapeutic agents, etc.); mental diseases, particularly anxiety disorders, stress-related disorders, affective disorders, psychological development disorders and schizophrenia; demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis; attenuation of morphine withdrawal; oedema, such as oedema caused by thermal injury; small cell carcinomas, particularly small cell lung cancer (SCLC); hypersensitivity disorders such as poison ivy; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; reflex sympathetic dystrophy such as shoulder/hand syndrome; addiction disorders such as alcoholism; stress related somatic disorders; rheumatic diseases such as fibrositis; aggressive behaviour, optionally taking an antipsychotic agent together; mania or hypomania, optionally taking an antipsychotic agent together; symptoms associated with Premenstrual Syndrome (PMS) (PMS is also now referred to as Late Luteal Phase Syndrome (LLS); psychosomatic disoredrs; psychoimmunologic disoredrs; attetion deficit disoredrs (ADD) with or without hyperactivity; and the like.

Furthermore, the object compound (I) and a pharmaceutically acceptable salt thereof of the present invention are Central Nervous System (CNS) penetrant.

For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compound, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable

for oral, parenteral, external including topical, enternal, intravenous, intramuscular, inhalant, nasal, intraarticular, intraspinal, transtracheal or transocular administration. The pharmaceutical preparations may be solid, semi-solid or solutions such as capsules, tablets, pellets, dragees, powders, granules, suppositories, ointments, creams, lotions, inhalants, injections, cataplasms, gels, tapes, eye drops, solution, syrups, aerosols, suspension, emulsion, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compound (I) will vary depending upon the age and condition of a patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating Tachykinin-mediated diseases such as asthma and the like. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

In order to show the utility of the object compound (I) and a pharmaceutically acceptable salt thereof, the pharmacological test data of some representative compounds of the present invention is shown in the following.

A. Evaluation of NK_1 antagonist transport efficiency to the central nervous system using a h-NK_1 receptor binding assay

[1] Test Method

(1) Administration of test compound and extraction of the compound from brain

Male SD rats were given an i.v. injection of a solution containing a test compound (1 mg/kg). 5 Min later the

animals were anesthetized by ether, bled and perfused through the aorta asscendens with 20 ml of saline. The brain was rapidly removed, weighed and homogenized in 4 vol. ice-cold distilled water by using Polytoron (KINEMATICA). To extract the test compound, 500 µl of the homogenate, 100 µl of methanol, 500 µl of 0.1 N NaOH and 4 ml of ethyl acetate were mixed by shaking for 10 min at room temperature. The organic phase (2.5 ml) was recovered by centrifugation at 3,000 rpm for 10 min, dried and dissolved in dimethyl sulfoxide.

(2) h-NK_1 receptor binding assay

(a) Crude CHO cell membrane preparation

CHO cells permanently expressing h-NK_1 receptors were harvested and homogenized with a Dounce homogenizer at 4°C in a buffer (0.25 M sucrose, 25 mM Tris-HCl (pH 7.4), 10 mM $MgCl_2$, 1 mM EDTA, 5 µg/ml p-APMSF). The homogenate was centrifuged (500 x g, 10 min), and the pellet was resuspended in the same buffer, homogenized, and centrifuged. The two supernatants were combined and centrifuged (100,000 x g, 1 hour). The crude cell membranes thus isolated were resuspended in a buffer (25 mM Tris-HCl (pH 7.4), 10 mM $MgCl_2$, 1 mM EDTA, 5 µg/ml p-APMSF) and stored at -80° until use.

(b) ^{125}I-BH-Substance P binding to the prepared membrane

Cell membranes (6 µg/ml) were incubated with ^{125}I-BH-Substance P (0.1 nM) with or without the extracted compounds in 0.25 ml of a medium (50 mM Tris-HCl (ph 7.4), 5 mM $MnCl_2$, 20 µg/ml chymostatin, 40 µg/ml bacitracin, 4 µg/ml leupeptin, 5 µg/ml p-APMSF, 200 µg/ml BSA) at 22°C for 90 min. At the end of the incubation period, the contents were quickly filtered through a Blue Mat 11740 filter (pretreated with

0.1% polyethylenimine for 3 hours prior to use) by using SKATRON Cell Harvester. The filter was then washed with a washing buffer (50 mM Tris-HCl (pH 7.4), 5 mM $MnCl_2$). The radioactivity was counted by using an auto gamma counter (Packard RIASTAR 5420A). All data presented are specific binding defined as that displaceable by 3 μM unlabeled Substance P.

[II] Test Result

All of the following Test Compounds showed more than 80% inhibition rate of ^{125}I-BH-Substance P binding to h-NK_1 receptors at the dose of 1 mg/kg.

Test Compounds: The object compounds of the Examples 4-(1), 4-(2), 7 and 8

B. Emesis in the dog

[I] Test Method

Individually housed adult female dogs (8 to 15 kg) were given an i.v. injection of a solution containing a test compound. 5 Min later the emetic responses (retching and vomiting) were induced by administration of subcutaneous apomorphine (0.1 mg/0.5 ml/kg) and observed for the next 60 min. The timing and number of retches and vomits observed were recorded for each animal. An individual animal was tested with at least 10 days between experiments.

[II] Test Result

The following Test Compound showed 100% inhibition rate of emesis in the dog at the dose of 0.32 mg/kg.

Test compound: The object compound of the Example 4-(1)

mp: 125.0-130.0°C

IR (KBr): 3316, 3200-2500, 1714, 1652, 1544 cm^{-1}

NMR (DMSO-d_6, δ): 1.79 (3H, s), 2.76 (1H, dd, J=9.6 and 13.7Hz), 2.96 (1H, dd, J=4.8 and 13.7Hz), 3.74 (3H, s), 4.35-4.37 (1H, m), 5.02 (2H, s), 6.71 (1H, dd, J=1.8 and 8.2Hz), 6.86 (1H, d, J=1.8Hz), 6.92 (1H, d, J=8.2Hz), 7.31-7.45 (5H, m), 8.15 (1H, d, J=8.0Hz), 12.63 (1H, br s)

MASS (APCI): 344 $(M+H)^+$, 302

Preparation 97

(D)-N-Acetyl-4-benzyloxy-3-methoxy-D-phenylalanine

$[\alpha]_D^{26}$: -14.3° (C=0.5, DMF)

mp: 148.0-149.0°C

IR (KBr): 3324, 3200-2700, 1741, 1616, 1550, 1513, 1398 cm^{-1}

NMR (DMSO-d_6, δ): 1.79 (3H, s), 2.76 (1H, dd, J=9.2 and 13.9Hz), 2.97 (1H, dd, J=4.8 and 13.9Hz), 3.74 (3H, s), 4.31-4.42 (1H, m), 5.02 (2H, s), 6.71 (1H, dd, J=1.8 and 8.2Hz), 6.86 (1H, d, J=1.8Hz), 6.92 (1H, d, J=8.2Hz), 7.28-7.45 (5H, m), 8.14 (1H, d, J=8.2Hz), 12.85 (1H, br s)

MASS (APCI): 344 $(M+H)^+$, 372

Preparation 98

The following compound was obtained according to a similar manner to that of Preparation 17.

4-Hydroxy-3-methoxy-D-phenylalanine hydrochloride

mp: 188-200°C

IR (KBr): 3500-3150, 2700-2300, 1739, 1589, 1488 cm^{-1}

NMR (D_2O, δ): 3.13 (1H, dd, J=7.6 and 14.6Hz), 3.28 (1H, dd, J=5.8 and 14.6Hz), 3.85 (3H, s), 4.28 (1H, dd, J=5.8 and 7.6Hz), 6.77-6.95 (3H, m)

MASS (APCI): 212 $(M+H)^+$, (free)

Preparation 99

Di-tert-butyl dicarbonate (2.55 g) was added to a solution of 4-hydroxy-3-methoxy-D-phenylalanine hydrochloride (2.2 g) and triethylamine (2.9 ml) in a mixture of acetone (25 ml) and water (25 ml). After being stirred at room temperature for 5 hours, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was separated, dried over magnesium sulfate and evaporated under reduced pressure to give N-tert-butyloxycarbonyl-4-hydroxy-3-methoxy-D-phenylalanine (2.6 g) as an oil.

NMR ($CDCl_3$, δ): 1.42 (9H, s), 2.82-3.20 (2H, m), 3.83 (3H, s), 4.20-5.50 (2H, m), 6.56-6.68 (2H, m), 6.83 (1H, d, J=8.5Hz), 7.23 (1H, s)

MASS (APCI): 212 $(M+H-Boc)^+$, 195

Preparation 100

Benzyl bromide (2.34 ml, 19.8 ml) was added to a solution of N-tert-butyloxycarbonyl-4-hydroxy-3-methoxy-D-phenylalanine (3.44 g) and N,N-diisopropylethylamine (3.85 ml) in N,N-dimethylformamide (20 ml). After being stirred at room temperature for 6 hours, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was separated, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of hexane and ethyl acetate (4:1) to give (2R)-2-(tert-butyloxycarbonylamino)-3-(4-hydroxy-3-methoxyphenyl)propionic acid benzyl ester (2.98 g) as colorless powders.

IR (KBr): 3438, 3378, 2700-2300, 1725, 1683, 1521, 1488 cm^{-1}

NMR ($CDCl_3$, δ): 1.41 (9H, s), 3.03 (2H, d, J=5.8Hz), 3.76 (3H, s), 4.45-4.55 (1H, m), 4.95-5.05 (1H, m), 5.09 (1H, d, J=12.5Hz), 5.18 (1H, d, J=12.5Hz), 5.53 (1H, s), 6.56-6.68 (2H, m), 6.76 (1H, d, J=8.0Hz),

7.25-7.36 (5H, m)

MASS (APCI): 302 $(M+H-Boc)^+$

Preparation 101

4N Hydrogen chloride in 1,4-dioxane solution (9 ml) was added to an ice-cooled solution of (2R)-2-(tert-butyloxycarbonylamino)-3-(4-hydroxy-3-methoxyphenyl)propionic acid benzyl ester (2.90 g) in dichloromethane (29 ml). After being stirred at the same temperature for 2 hours, the mixture was concentrated under reduced pressure to give (2R)-2-amino-3-(4-hydroxy-3-methoxyphenyl)propionic acid benzyl ester hydrochloride (2.8 g) as an oil.

NMR (DMSO-d_6, δ): 3.00-3.10 (2H, m), 3.70 (3H, s), 4.31 (1H, t, J=6.2Hz), 5.18 (2H, s), 6.54 (1H, dd, J=1.7 and 8.0Hz), 6.68 (1H, d, J=8.0Hz), 6.81 (1H, d, J=1.7Hz), 7.29-7.39 (5H, m), 8.57 (3H, br s), 8.97 (1H, s)

MASS (APCI): 301 $(M+H)^+$ (free)

Preparation 102

The following compound was obtained according to a similar manner to that of Preparation 19.

(2R)-2-[N-(Chloroacetyl)amino]-3-(4-hydroxy-3-methoxyphenyl)propionic acid benzyl ester

Preparation 103

The following compound was obtained according to a similar manner to that of the first half of Preparation 20.

(2R)-2-[N-[(Benzylamino)acetyl]amino]-3-(4-hydroxy-3-methoxyphenyl)propionic acid benzyl ester

Preparation 104

The following compound was obtained according to a

similar manner to that of the second half of Preparation 20.

(3R)-1-Benzyl-3-(4-hydroxy-3-methoxybenzyl)piperazine-2,5-dione

$[\alpha]_D^{26}$: -5.2° (C=0.5, DMF)

mp: 225.0-226.0°C

IR (KBr): 3335, 1677, 1515, 1463, 1276, 1185 cm^{-1}

NMR (DMSO-d_6, δ): 2.73 (1H, d, J=17.2Hz), 2.78 (1H, dd, J=4.6 and 13.6Hz), 3.04 (1H, dd, J=4.6 and 13.6Hz), 3.42 (1H, d, J=17.2Hz), 3.66 (3H, s), 4.28 (1H, m), 4.27 (1H, d, J=14.6Hz), 4.47 (1H, d, J=14.6Hz), 6.43 (1H, dd, J=1.8 and 8.0Hz), 6.54 (1H, d, J=8.0Hz), 6.67 (1H, d, J=1.8Hz), 7.05-7.31 (5H m), 8.31 (1H, br s), 8.84 (1H, s)

MASS (APCI): 341 $(M+H)^+$

Preparation 105

Lithium aluminum hydride (614 mg) was added to a suspension of (3R)-1-benzyl-3-(4-hydroxy-3-methoxybenzyl)piperazine-2,5-dione (1.1 g) in tetrahydrofuran (40 ml) at room temperature. After being stirred under reflux for 5 hours, the reaction mixture was treated with 2N sodium hydroxide (5 ml) under nitrogen atmosphere. The whole mixture was diluted with water (40 ml) and thereto 3,5-bis(trifluoromethyl)benzoyl chloride (1.6 ml) was added dropwise under ice-cooling. After being stirred for 30 minutes, the resulting mixture was extracted with ethyl acetate. The organic layer was separated, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of hexane and ethyl acetate (4:1) to give the objective (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(4-hydroxy-3-methoxybenzyl)piperazine and its 3,5-bis(trifluoromethyl)benzoate, which was converted to the objective compound by treatment with a mixture of 1N sodium

hydroxide and methanol.

NMR ($CDCl_3$, δ): 2.20-4.55 (14H, m), 6.20-7.90 (12H, m)

MASS (APCI): 553 $(M+H)^+$

Preparation 106

Trifluoromethane sulfonic acid anhydride (5.25 ml) was added dropwise over 30 minutes to an ice-cooled solution of (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(4-hydroxy-3-methoxybenzyl)piperazine (14.3 g) and 4-(dimethylamino)pyridine (0.47 g) and 2,6-lutidine (3.6 ml) in dichloromethane (150 ml) below 10°C. After being stirred at the same temperature for 2 hours, the reaction mixture was poured into water. The pH of the whole mixture was adjusted to 7 with diluted hydrochloric acid and the organic layer was separated, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of toluene and ethyl acetate (100:1~5:1) to give the objective trifluoromethanesulfonic acid 4-[[(2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-benzylpiperazin-2-yl]methyl]-2-methoxyphenyl ester as an oil.

Preparation 107

Carbon monoxide was introduced by bubbling to a mixture of trifluoromethanesulfonic acid 4-[[(2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-benzylpiperazin-2-yl]methyl]-2-methoxyphenyl ester (15.0 g), palladium acetate (150 mg), 1,3-bis(diphenylphosphino)propane (275 mg) and triethylamine (4.28 ml) in a mixed solvent of methanol (30 ml) and N,N-dimethylformamide (75 ml) at room temperature for 1 hour. The mixture was warmed to 70°C and stirred under carbon monoxide atmosphere for 3 hours. The resulting mixture was filtered through Celite® and the residue was washed with ethyl acetate. The filtrate and washings were combined and evaporated under reduced pressure. The residue was dissolved

into ethyl acetate and the solution was washed with water and brine successively, dried over magnesium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixed solvent of toluene and hexane as eluent. The fractions containing the objective compound was collected and evaporated under reduced pressure to give a syrup, which was treated with 4N hydrogen chloride in ethyl acetate to give a powder of 4-[[(2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-benzylpiperazin-2-yl]methyl]-2-methoxybenzoic acid methyl ester hydrochloride (7.71 g).

mp: 100-102°C

IR (KBr): 3335, 1720, 1648, 1614, 1459, 1427, 1185 cm^{-1}

NMR (DMSO-d_6, δ): 2.95-5.20 (11H, m), 3.41 (3H, s), 3.75 (3H, s), 6.40-8.25 (11H, m), 11.50-11.80 (1H, m)

MASS (API-ES): 617 $(M+Na, free)^+$, 595 $(M+H, free)^+$

Preparation 108

The following compound was obtained according to a similar manner to that of Preparation 22.

4-[[(2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-benzylpiperazin-2-yl]methyl]-2-hydroxybenzoic acid methyl ester

IR (Neat): 1677, 1643, 1438, 1280 cm^{-1}

NMR ($CDCl_3$, δ): 2.00-5.10 (11H, m), 3.93 (3H, s), 6.20-7.90 (11H, m), 10.71 (1H, br s)

MASS (API-ES): 603 $(M+Na)^+$, 581 $(M+H)^+$

Preparation 109

tert-Butyldimethylsilyl chloride (2.34 g) was added to a solution of 4-[[(2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-piperazin-2-yl]methyl]-2-hydroxybenzoic acid methyl ester (2.56 g), 4-(dimethylamino)pyridine (126 mg) and triethylamine (2.51 ml) in dichloromethane (50 ml) at room

temperature. After stirring at room temperature for 15 hours, additional triethylamine (2.51 ml) and tert-butyldimethylsilyl chloride (2.34 g) were added and the whole mixture was stirred for further 1 day. Water (200 ml) was added to the mixture, and the resulting mixture was extracted with dichloromethane. The organic extracts were washed with water and brine successively, dried over magnesium sulfate, and evaporated under reduced pressure to give crude oil. The oil was purified by column chromatography on silica gel using a mixed solvent of dichloromethane and methanol to give 4-[[(2R)-1-[3,5-bis(trifluoromethyl)benzoyl]piperazin-2-yl]-methyl]-2-(tert-butyldimethylsilyloxy)benzoic acid methyl ester (1.72 g).

IR (Neat): 2955, 1727, 1639, 1436, 1280 cm^{-1}

NMR ($CDCl_3$, δ): 0.10-0.30 (6H, m), 1.00 (9H, s), 2.80-5.10 (9H, m), 3.85 (3H, s), 6.30-7.90 (6H, m)

MASS (APCI): 605 $(M+H)^+$, 573, 491

Preparation 110

To a solution of (2R)-2-tert-butoxycarbonylamino-3-(4-methoxyphenyl)propionic acid (5.14 g) in dichloromethane (50 ml) was added triethylamine (8.49 ml), N-benzylglycine benzyl ester hydrochloride (5.08 g), and 2-chloro-1-methylpyridinium iodide (4.89 g) under ice-bath cooling. After being stirred at room temperature 90 minutes, the reaction mixture was concentrated under reduced pressure, and ethyl acetate (50 ml) and water (50 ml) were added to the residue with stirring, adjusted pH 1 with diluted hydrochloric acid. The organic layer was separated, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (100 g) using a mixed solvent of toluene and ethyl acetate (10:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give N-benzyl-N-(benzyloxycarbonylmethyl)-(2R)-2-(tert-

butoxycarbonylamino)-3-(4-methoxyphenyl)propionamide (8.57 g) as a syrup.

$[\alpha]_D^{24.0}$: +6.60° (C=0.50, MeOH)

IR (Neat): 3300, 1740, 1700, 1650, 1240 cm^{-1}

NMR (DMSO-d_6, δ): 1.27 and 1.31 (9H, s, s), 2.76 (2H, m), 3.69 and 3.70 (3H, s, s), 3.95-4.90 (5H, m), 5.13 (2H, m), 6.70-7.36 (15H, m)

MASS (APCI): 533 $(M+H)^+$

Preparation 111

4N Hydrogen chloride in 1,4-dioxane solution (48 ml) was added dropwise to a solution of N-benzyl-N-benzyloxycarbonylmethyl-(2R)-2-(tert-butoxycarbonylamino)-3-(4-methoxyphenyl)propionamide (8.48 g) in dichloromethane (48 ml) under ice-bath cooling. After being stirred for 2 hours at the same temperature, the reaction mixture was concentrated under reduced pressure. The residue was added to aqueous sodium bicarbonate solution (50 ml) and dichloromethane (50 ml), and the organic layer was separated, washed with brine, dried over sodium sulfate, and evaporated under reduced pressure to give a powder of (3R)-1-benzyl-3-(4-methoxybenzyl)piperazine-2,5-dione (3.65 g).

$[\alpha]_D^{27.9}$: -38.6° (C=0.50, MeOH)

IR (Nujol): 3250, 1680, 1640, 1245 cm^{-1}

NMR (DMSO-d_6, δ): 2.60 (1H, d, J=17Hz), 2.80 (1H, dd, J=4.7 and 14Hz), 3.09 (1H, dd, J=3.8 and 14Hz), 3.46 (1H, d, J=17Hz), 3.67 (3H, s), 4.11 (1H, d, J=14Hz), 4.22 (1H, br), 4.65 (1H, d, J=14Hz), 6.63 (2H, d, J=8.7Hz), 6.93 (2H, d, J=8.7Hz), 7.10-7.40 (5H, m), 8.30 (1H, br)

MASS (APCI): 325 $(M+H)^+$

Preparation 112

Under nitrogen atmosphere, to a suspension of lithium aluminum hydride (0.85 g) in tetrahydrofuran (65 ml) was

added (3R)-1-benzyl-3-(4-methoxybenzyl)piperazine-2,5-dione (3.65 g) portionwise under ice-bath cooling. The reaction mixture was refluxed with stirring for one hour. After cooling, it was quenched by sequential addition of water (0.85 ml), 15% aqueous sodium hydroxide (0.85 ml), and water (2.5 ml) and the whole was stirred at room temperature for 30 minutes. The resulting insoluble material was removed by filtration, and the filtrate was added to a mixture of ethyl acetate (50 ml) and brine (70 ml). The organic layer was separated, dried over magnesium sulfate, and concentrated under reduced pressure to give (2R)-2-(4-methoxybenzyl)-4-benzylpiperazine (3.51 g) as a syrup.

IR (Neat): 3250, 1240 cm^{-1}

NMR (DMSO-d_6, δ): 1.60-2.00 (4H, m), 2.40-2.90 (5H, m), 3.30-3.50 (2H, m), 3.70 (3H, s), 6.81 (2H, d, J=8.6Hz), 7.07 (2H, d, J=8.6Hz), 7.15-7.40 (6H, m)

MASS (APCI): 297 $(M+H)^+$

Preparation 113

To a solution of 3,5-bis(trifluoromethyl)benzoic acid (3.04 g) and pyridine (0.030 ml) in tetrahydrofuran (9 ml) was added dropwise oxalyl chloride (1.80 g) over 5 minutes, and the reaction mixture was heated at 55°C with stirring for one hour. After cooling, the solution was added dropwise to a solution of (2R)-2-(4-methoxybenzyl)-4-benzylpiperazine (3.47 g) and triethylamine (3.55 g) in dichloromethane (35 ml) below 5°C over 30 minutes under nitrogen atmosphere. The reaction mixture was stirred at room temperature for one hour, and concentrated under reduced pressure. To the residue were added ethyl acetate (40 ml) and water (20 ml) with stirring. The organic layer was separated, washed with brine, and dried over magnesium sulfate. After removal of the solvent by evaporation, the resulting residue was purified by column chromatography on silica gel (70 g) using a mixed solvent of toluene and ethyl acetate (5:1). The

fractions containing the objective compound were collected and evaporated under reduced pressure to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(4-methoxybenzyl)-4-benzylpiperazine (5.03 g) as syrup.

$[\alpha]_D^{28.0}$: -21.4° (C=0.50, MeOH)

IR (Neat): 1740, 1640, 1270 cm^{-1}

NMR (DMSO-d_6, δ): 1.70-2.40 (3H, m), 2.60-3.80 (11H, m), 6.60-7.60 (10H, m), 7.65-8.55 (2H, m)

MASS (APCI): 537 $(M+H)^+$

Preparation 114

To a solution of (2R)-1-[3,5-bis(trifluoromethyl)-benzoyl]-2-(4-methoxybenzyl)-4-benzylpiperazine (4.90 g) in ethanol (50 ml) were added water (5 ml), ammonium formate (1.44 g), and 10% palladium on activated carbon [50% wet] (0.49 g) under nitrogen atmosphere. The reaction mixture was heated at 60°C with stirring for 2 hours. Insoluble material was removed by filtration, and the filtrate was concentrated under reduced pressure. Ethyl acetate (40 ml) and water (40 ml) were added to the residue, and the organic layer was separated, washed with brine, and dried over magnesium sulfate. After removal of the solvent by evaporation, the resulting residue was purified by column chromatography on silica gel (70 g) using a mixed solvent of ethyl acetate and methanol (10:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(4-methoxybenzyl)piperazine (3.18 g) as syrup.

$[\alpha]_D^{28.1}$: -32.6° (C=0.50, MeOH)

IR (Neat): 3300, 1630, 1280 cm^{-1}

NMR (DMSO-d_6, δ): 2.40-3.55 (9H, m), 3.72 (3H, s), 6.70-8.45 (7H, m)

MASS (APCI): 447 $(M+H)^+$

Preparation 115

The following compounds were obtained according to a similar manner to that of Preparation 56.

(1) (2R)-4-Benzyl-1-(tert-butoxycarbonyl)-2-[4-(trifluoromethyl)benzyl]piperazine
NMR ($CDCl_3$, δ): 1.36 (9H, s), 1.98 (1H, dd, J=11.5 and 3.7Hz), 2.10 (1H, td, J=12.0 and 3.4Hz), 2.58 (1H, d, J=11.5Hz), 2.83-3.13 (3H, m), 3.20 (1H, td, J=12.8 and 3.4Hz), 3.26 (1H, d, J=12.8Hz), 3.58 (1H, d, J=12.8Hz), 3.80-4.30 (2H, m), 7.12 (2H, d, J=7.7Hz), 7.26-7.42 (7H, m)
MASS (APCI): 435 $(M+H)^+$

(2) (2R)-4-Benzyl-2-(4-fluoro-3-methoxybenzyl)-1-(tert-butoxycarbonyl)piperazine
IR (Neat): 1516, 1458, 1400, 1327, 1275, 1217, 1169 cm^{-1}
NMR ($CDCl_3$, δ): 1.39 (9H, s), 1.95-2.13 (2H, m), 2.60-3.24 (5H, m), 3.32-3.57 (2H, m), 3.79 (3H, s), 3.90-4.14 (2H, m), 6.52-7.35 (8H, m)
MASS (APCI): 415 $(M+H)^+$

(3) (2R)-4-Benzyl-1-(tert-butoxycarbonyl)-2-[4-chloro-3-(tert-butyldimethylsilyloxy)benzyl]piperazine
IR (Neat): 1695, 1480, 1415, 1250, 1170 cm^{-1}

(4) (3S,4S)-1-(tert-Butoxycarbonyl)pyrrolidine-3,4-diol
mp: 156-158°C
IR (KBr): 3398, 3334, 1662, 1431, 1174, 1122, 1082, 985 cm^{-1}
NMR (DMSO-d_6, δ): 1.42 (9H, s), 3.10 (2H, br d, J=11.3Hz), 3.25-3.44 (2H, m), 3.86 (2H, br s), 5.05 (2H, d, J=3.2Hz)
MASS (ES+): 429.3 $(2M+Na)^+$, 226.2 $(M+Na)^+$ (free)

Preparation 116

The following compounds were obtained according to a similar manner to that of Preparation 37.

(1) 4-[[(2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]piperazin-2-yl]methyl]-2-hydroxybenzoic acid methyl ester
IR (Neat): 3083, 1677, 1639, 1438, 1280 cm^{-1}

(2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[3-(tert-butyldimethylsilyloxy)-4-chlorobenzyl]piperazine
mp: 95-97°C
IR (KBr): 1954, 1628, 1481, 1437 cm^{-1}
NMR ($CDCl_3$, δ): 0.17 (3H, s), 0.20 (3H, s), 1.01 (9H, s), 2.50-5.10 (9H, m), 6.30-7.70 (5H, m), 7.87 (1H, s)
MASS (APCI): 581 $(M+H)^+$

(3) (2R)-2-[3-(tert-Butyldimethylsilyloxy)-4-chlorobenzyl]-1-[3-chloro-5-(trifluoromethyl)benzoyl]piperazine
IR (Neat): 2954, 2933, 1635, 1483, 1419 cm^{-1}
NMR ($CDCl_3$, δ): 0.18 (3H, s), 0.21 (3H, s), 1.02 (9H, s), 2.50-5.20 (9H, m), 6.20-7.70 (6H, m)
MASS (APCI): 547 $(M+H)^+$

(4) (2R)-1-(tert-Butoxycarbonyl)-2-[4-chloro-3-(tert-butyldimethylsilyloxy)benzyl]piperazine
NMR (DMSO-d_6, δ): 0.99 (9H, s), 1.24 (9H, s), 2.15 (6H, s), 2.20-4.10 (9H, m), 6.78-7.33 (3H, m)
MASS (APCI): 441 $(M+H)^+$

Preparation 117

The following compounds were obtained according to a similar manner to that of Preparation 24.

(1) (2R)-1-(tert-Butoxycarbonyl)-2-[4-(trifluoromethyl)-benzyl]piperazine

mp: 61-62°C
IR (KBr): 2981, 2952, 1682, 1417, 1330 cm^{-1}
NMR ($CDCl_3$, δ): 1.33 (9H, s), 2.67-4.40 (9H, m),
7.35 (2H, d, J=8.0Hz), 7.54 (2H, d, J=8.0Hz)
MASS (ESI): 345.3 $(M+H)^+$, 289.2 $(M-Bu)^+$

(2) (2R)-2-(4-Fluoro-3-methoxybenzyl)-1-(tert-butoxycarbonyl)piperazine
IR (Neat): 1689, 1515, 1414, 1273, 1165, 1115 cm^{-1}
NMR ($CDCl_3$, δ): 1.38 (9H, s), 2.70-3.14 (8H, m),
3.87 (3H, s), 3.88-4.18 (2H, m), 6.74-7.26 (3H, m)
MASS (APCI): 225 $(M-Boc+1)^+$, 269 $(M-tBu+1)^+$

(3) (2R)-1-[3-(Dimethylsulfamoyl)-5-(trifluoromethyl)-benzoyl]-2-[4-(trifluoromethyl)benzyl]piperazine
IR (KBr): 2956, 1639, 1462, 1423, 1329 cm^{-1}
NMR ($CDCl_3$, δ): 2.60-5.20 (9H, m), 2.72 (6H, s),
7.00-7.60 (5H, m), 7.67 (1H, s), 8.00 (1H, s)
MASS (APCI): 524 $(M+H)^+$

(4) (2R)-1-[3-Methylsulfonyl-5-(trifluoromethyl)benzoyl]-2-[4-(trifluoromethyl)benzyl]piperazine hydrochloride
mp: 94.5-101°C
IR (KBr): 3433, 1645 cm^{-1}
NMR (DMSO-d_6, δ): 2.80-5.30 (12H, m), 7.00-8.31 (7H, m)
MASS (APCI): 495 $(M+H)^+$ (free)

(5) (2R)-2-(3-tert-Butyldimethylsilyloxy-4-methylbenzyl)-1-[3-methoxy-5-(trifluoromethyl)benzoyl]piperazine
IR (KBr): 2956, 2935, 1641, 1606 cm^{-1}
NMR ($CDCl_3$, δ): 0.14, 0.17 (6H, s), 0.99 (9H, s),
2.15 (3H, s), 2.50-5.20 (9H, m), 3.81 (3H, s),
6.75-7.13 (6H, m)
MASS (APCI): 523 $(M+H)^+$

Preparation 118

The following compounds were obtained according to a similar manner to that of Example 1 using N,N-diisopropylethylamine instead of potassium carbonate as a base.

(1) (2R)-1-(tert-Butoxycarbonyl)-4-[2-(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)ethyl]-2-[4-(trifluoromethyl)-benzyl]piperazine
IR (KBr): 2974, 2935, 2814, 1693 cm^{-1}
NMR ($CDCl_3$, δ): 1.35 (9H, s), 2.04-2.17 (2H, m), 2.50-4.30 (17H, m), 7.07 (1H, dd, J=4.8 and 7.6Hz), 7.27-7.34 (3H, m), 7.50 (2H, d, J=8.0Hz), 8.40 (1H, d, J=4.8Hz)
MASS (APCI): 505 $(M+H)^+$

(2) (2R)-1-(tert-Butoxycarbonyl)-4-[2-(cis-2,6-dimethylmorpholino)ethyl]-2-[4-(trifluoromethyl)benzyl]-piperazine
IR (Neat): 2974, 1693, 1680 cm^{-1}
NMR ($CDCl_3$, δ): 1.19, 1.20 (6H, d, J=6.2Hz), 1.32 (9H, s), 2.02-2.21 (4H, m), 2.71-3.31 (11H, m), 3.90-4.50 (4H, m), 7.34 (2H, d, J=7.9Hz), 7.54 (2H, d, J=7.9Hz)
MASS (APCI): 486 $(M+H)^+$

(3) (2R)-1-(tert-Butoxycarbonyl)-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]-2-[4-(trifluoromethyl)-benzyl]piperazine
IR (Neat): 3438, 2816, 1691 cm^{-1}
NMR ($CDCl_3$, δ): 1.33 (9H, s), 2.02-4.30 (22H, m), 3.37 (3H, s), 7.35 (2H, d, J=8.0Hz), 7.54 (2H, d, J=8.0Hz)
MASS (APCI): 502 $(M+H)^+$

(4) (2R)-2-(4-Fluoro-3-methoxybenzyl)-1-(tert-butoxycarbonyl)-4-[2-(cis-2,6-dimethylmorpholino)ethyl]-piperazine

IR (Neat): 1515, 1458, 1414, 1367, 1323, 1115, 1086 cm^{-1}

NMR ($CDCl_3$, δ): 1.14 (6H, d, J=1.2Hz), 1.40 (9H, s), 1.70-2.10 (4H, m), 2.36-3.20 (12H, m), 3.61-4.18 (3H, m), 3.88 (3H, s), 6.74-7.02 (3H, m)

MASS (APCI): 466 $(M+H)^+$

(5) (2R)-2-(4-Fluoro-3-methoxybenzyl)-1-(tert-butoxycarbonyl)-4-[2-[(2S)-2-(methoxymethyl)morpholino]-ethyl]piperazine

IR (Neat): 1516, 1456, 1414, 1273, 1165, 1111, 1036 cm^{-1}

NMR ($CDCl_3$, δ): 1.40 (9H, s), 1.90-4.25 (22H, m), 3.38 (3H, s), 3.87 (3H, s), 6.69-7.27 (3H, m)

MASS: 482 $(M+H)^+$

(6) (2R)-2-(4-Fluoro-3-methoxybenzyl)-1-(tert-butoxycarbonyl)-4-[2-(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)ethyl]piperazine

NMR (DMSO-d_6, δ): 1.40 (9H, s), 1.99-2.15 (2H, m), 2.51-3.18 (14H, m), 3.67-4.18 (3H, m), 3.86 (3H, s), 6.73-8.40 (6H, m)

MASS: 485 $(M+H)^+$

(7) (2R)-1-(tert-Butoxycarbonyl)-2-(4-chloro-3-hydroxybenzyl)-4-[2-[(2S)-2-(methoxymethyl)morpholino]-ethyl]piperazine

Preparation 119

The following compounds were obtained according to a similar manner to that of Preparation 41.

(1) (2R)-4-Benzyl-1-[3-(dimethylsulfamoyl)-5-(trifluoro-methyl)benzoyl]-2-[4-(trifluoromethyl)benzyl]piperazine

IR (Neat): 1645, 1456, 1419, 1319 cm^{-1}

NMR ($CDCl_3$, δ): 2.00-2.40 (2H, m), 2.70-5.10 (9H, m), 2.73 (6H, s), 6.90-7.60 (10H, m), 7.73 (1H, s), 8.01 (1H, s)

MASS (APCI): 614 $(M+H)^+$

(2) (2R)-4-Benzyl-1-[3-methylsulfonyl-5-(trifluoromethyl)benzoyl]-2-[4-(trifluoromethyl)benzyl]piperazine

NMR ($CDCl_3$, δ): 2.00-2.40 (2H, m), 2.70-3.71 (8H, m), 3.06 (3H, s), 4.50-5.10 (1H, m), 6.80-7.60 (10H, m), 7.86 (1H, s), 8.19 (1H, s)

MASS (APCI): 585 $(M+H)^+$

(3) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-benzyl-2-[3-(tert-butyldimethylsilyloxy)-4-chlorobenzyl]piperazine

IR (Neat): 2935, 2860, 2812, 1645, 1483, 1423 cm^{-1}

NMR ($CDCl_3$, δ): 0.10-0.30 (6H, br), 1.00 (9H, s), 1.80-5.10 (11H, m), 6.20-8.00 (10H, m), 7.87 (1H, s)

MASS (APCI): 671 $(M+H)^+$

(4) (2R)-4-Benzyl-2-[3-(tert-butyldimethylsilyloxy)-4-chlorobenzyl]-1-[3-chloro-5-(trifluoromethyl)benzoyl]-piperazine

IR (Neat): 2935, 1641, 1483, 1417 cm^{-1}

NMR ($CDCl_3$, δ): 0.10-0.30 (6H, br), 1.01 (9H, s), 1.80-5.00 (11H, m), 6.20-7.70 (10H, m), 7.59 (1H, s)

MASS (APCI): 637 $(M+H)^+$

(5) (2R)-4-Benzyl-2-[3-(tert-butyldimethylsilyloxy)-4-methylbenzyl]-1-[3-methoxy-5-(trifluoromethyl)benzoyl]-piperazine

IR (KBr): 1643, 1464, 1421, 1267 cm^{-1}

NMR ($CDCl_3$, δ): 0.09 (6H, br s), 0.98 (9H, s), 2.04-2.21 (2H, m), 2.14 (3H, s), 2.60-5.10 (12H, m), 6.24-7.36 (11H, m)

MASS (APCI): 613 $(M+H)^+$

Preparation 120

The following compounds were obtained according to a similar manner to that of Preparation 59.

(1) (2R)-4-[2-(5,6,7,8-Tetrahydro-1,6-naphthyridin-6-yl)-ethyl]-2-[4-(trifluoromethyl)benzyl]piperazine tetrahydrochloride

NMR (DMSO-d_6, δ): 3.03-4.00 (19H, m), 7.57 (2H, d, J=8.1Hz), 7.75 (2H, d, J=8.1Hz), 7.85 (1H, dd, J=7.7 and 5.6Hz), 8.29 (1H, d, J=7.7Hz), 8.78 (1H, d, J=5.6Hz)

MASS (APCI): 405 $(M+H)^+$ (free)

(2) (2R)-4-[2-(cis-2,6-Dimethylmorpholino)ethyl]-2-[4-(trifluoromethyl)benzyl]piperazine trihydrochloride

mp: >250°C

IR (KBr): 2563, 2426, 1456, 1327 cm^{-1}

NMR ($CDCl_3$, δ): 1.11 (6H, d, J=6.2Hz), 2.59-4.50 (19H, m), 7.56 (2H, d, J=8.1Hz), 7.75 (2H, d, J=8.1Hz)

MASS (APCI): 386 $(M+H)^+$ (free)

(3) (2R)-4-[2-[(2S)-2-(Methoxymethyl)morpholino]ethyl]-2-[4-(trifluoromethyl)benzyl]piperazine trihydrochloride

mp: 80-95°C

IR (KBr): 1695, 1516 cm^{-1}

NMR (DMSO-d_6, δ): 2.80-4.60 (25H, m), 7.56 (2H, d, J=8.1Hz), 7.75 (2H, d, J=8.1Hz)

MASS (APCI): 402 $(M+H)^+$ (free)

(4) (2R)-2-(4-Fluoro-3-methoxybenzyl)-4-[2-(cis-2,6-dimethylmorpholino)ethyl]piperazine trihydrochloride

IR (KBr): 1610, 1517, 1452, 1425, 1367, 1326, 1274 cm^{-1}

NMR (DMSO-d_6, δ): 1.11 (6H, d, J=6.0Hz), 2.49-4.40 (21H,

m), 3.86 (3H, s), 6.87-7.24 (3H, m), 9.55-10.06 (2H, m)
MASS: 366 $(M+H)^+$ (free)

(5) (2R)-2-(4-Fluoro-3-methoxybenzyl)-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]piperazine trihydrochloride
IR (KBr): 3465, 3435, 3400, 1615, 1515, 1455, 1270, 1235 cm^{-1}
NMR (DMSO-d_6, δ): 2.65-4.20 (22H, m), 3.27 (3H, s), 3.86 (3H, s), 6.82-7.23 (3H, m)
MASS (APCI): 382 $(M+H)^+$ (free)

(6) (2R)-2-(4-Fluoro-3-methoxybenzyl)-4-[2-(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)ethyl]piperazine tetrahydrochloride
IR (KBr): 1515, 1464, 1269, 1153, 1095 cm^{-1}
NMR ($CDCl_3$, δ): 2.60-4.50 (22H, m), 3.84 (3H, s), 6.85-10.0 (8H, m)
MASS: 385 $(M+H)^+$ (free)

(7) (2R)-2-(4-Chloro-3-hydroxybenzyl)-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]piperazine trihydrochloride
IR (KBr): 1645, 1450, 1425, 1370, 1236, 1140 cm^{-1}
NMR (DMSO-d_6, δ): 2.64-4.50 (22H, m), 3.27 (3H, s), 6.71-7.32 (3H, s)
MASS (APCI): 384 $(M+H)^+$ (free)

(8) (3S,4S)-3,4-Dimethoxypyrrolidine hydrochloride
mp: 168°C
IR (KBr): 3464, 2900-2350, 1198, 1109, 1065, 1024 cm^{-1}
NMR (DMSO-d_6, δ): 3.05-3.35 (4H, m), 3.31 (6H, s), 4.00 (2H, d, J=3.5Hz), 9.67 (2H, br s)
MASS (APCI): 132 $(M+H)^+$ (free)

Preparation 121

2-Bromoethanol (310 mg) was added to a solution of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[4-(trifluoromethyl)-benzyl]piperazine (1 g) in acetonitrile (10 ml). The reaction mixture was stirred at 70°C for 19 hours. The mixture was filtered, and the residue on filter was washed with dichloromethane twice. The filtrate and combined washings were concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with methanol in dichloromethane (2% then 5%) to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-(2-hydroxyethyl)-2-[4-(trifluoromethyl)benzyl]piperazine (927 mg) as an amorphous powder.

IR (Neat): 3462, 3435, 2949, 2817, 1637, 1439 cm^{-1}

NMR ($CDCl_3$, δ): 2.1-5.2 (14H, m), 6.9-8.0 (7H, m)

MASS (APCI): 529 $(M+H)^+$

Preparation 122

The following compound was obtained according to a similar manner to that of Preparation 121.

(2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-fluoro-3-methoxybenzyl)-4-(2-hydroxyethyl)piperazine

IR (Neat): 2945, 2817, 1639, 1518, 1442 cm^{-1}

NMR ($CDCl_3$, δ): 2.20-5.10 (13H, m), 4.52 (3H, s), 6.30-7.89 (6H, m)

MASS (APCI): 509 $(M+H)^+$

Preparation 123

The following compounds were obtained according to a similar manner to that of Preparation 9.

(1) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-(2-chloroethyl)-2-[4-(trifluoromethyl)benzyl]piperazine hydrochloride

IR (KBr): 3437, 3429, 2561, 1649, 1427 cm^{-1}

NMR (DMSO-d_6, δ): 2.20-5.40 (13H, m), 7.10-8.30 (7H, m)
MASS (APCI): 547 $(M+H)^+$ (free)

(2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-(2-chloroethyl)-2-(4-fluoro-3-methoxybenzyl)piperazine hydrochloride
mp: 75-79°C
IR (KBr): 1647, 1518, 1427 cm^{-1}
NMR (DMSO-d_6, δ): 2.75-5.20 (13H, m), 4.49 (3H, s), 6.50-8.23 (6H, m)
MASS (APCI): 527 $(M+H)^+$ (free)

Preparation 124

The following compound was obtained according to a similar manner to that of Preparation 57.

(2R)-4-Benzyl-2-[3-(tert-butyldimethylsilyloxy)-4-methylbenzyl]piperazine
IR (Neat): 2952, 2933, 2856, 1504 cm^{-1}
NMR (DMSO-d_6, δ): 0.21 (6H, s), 1.02 (9H, s), 1.66-2.00 (2H, m), 2.13 (3H, s), 2.49-2.85 (4H, m), 3.37-3.41 (5H, m), 6.63 (1H, s), 6.69 (1H, d, J=7.6Hz), 7.05 (1H, d, J=7.6Hz), 7.25-7.40 (5H, m)
MASS (ESI+): 411.4 $(M+H)^+$

Preparation 125

A solution of (2S,4R)-1-benzyl-4-hydroxy-2-(hydroxymethyl)pyrrolidine (1.49 g) in N,N-dimethylformamide (10 ml) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 689 mg) in N,N-dimethylformamide (5 ml) dropwise at ambient temperature. The reaction mixture was stirred at the same temperature for 1 hour. To the reaction mixture was added methyl iodide (2.55 g) in N,N-dimethylformamide (3 ml) dropwise. After stirring at ambient temperature for 2 hours, the reaction mixture was poured into

ice water, and the whole was extracted with ethyl acetate twice. The combined organic layer was washed successively with a mixture of saturated aqueous sodium bicarbonate solution and 5% aqueous sodium thiosulfate solution, and saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with methanol in dichloromethane 1% then 2% to give (2S,4R)-1-benzyl-4-methoxy-2-(methoxymethyl)pyrrolidine (1.07 g) as an oil.

IR (Neat): 2877, 2817, 1452 cm^{-1}

NMR ($CDCl_3$, δ): 1.79-2.02 (2H, m), 2.26 (1H, dd, J=9.9 and 5.6Hz), 2.88-3.01 (1H, m), 3.19-3.49 (4H, m), 3.25 (3H, s), 3.35 (3H, s), 3.86 (1H, m), 4.10 (1H, d, J=13.1Hz), 7.20-7.33 (5H, m)

MASS (APCI): 236 $(M+H)^+$

Preparation 126

The following compounds were obtained according to a similar manner to that of Preparation 15.

(1) (2S,4R)-4-Methoxy-2-(methoxymethyl)pyrrolidine

IR (Neat): 3342, 2881, 1668, 1444 cm^{-1}

NMR ($CDCl_3$, δ): 1.55 (1H, m), 1.93 (1H, dd, J=13.6 and 7.1Hz), 2.88-3.09 (2H, m), 3.24-3.52 (3H, m), 3.29 (3H, s), 3.36 (3H, s), 3.89 (1H, m)

MASS (APCI): 146 $(M+H)^+$

(2) (3S,4S)-Pyrrolidine-3,4-diol hydrochloride

mp: 69-73°C

IR (KBr): 3400, 1622, 1442, 1238, 1109, 1030, 989 cm^{-1}

NMR (DMSO-d_6-D_2O, δ): 3.05 (2H, d, J=12.1Hz), 3.28 (2H, dd, J=12.1 and 3.2Hz), 4.10 (2H, d, J=3.2Hz)

MASS (APCI): 104 $(M+H)^+$ (free)

(3) cis-2,6-Dimethoxymethylpiperidine hydrochloride
mp: 200-202°C
IR (KBr): 3402, 2941, 2821, 2735, 1645, 1516, 1456 cm^{-1}
NMR (DMSO-d_6, δ): 1.30-1.90 (6H, m), 3.10-3.40 (2H, m), 3.30 (6H, s), 3.54 (4H, d, J=5.3Hz)
MASS (APCI): 1.74 $(M+H)^+$ (free)

(4) cis-3,5-Dimethoxymethylpiperidine hydrochloride
mp: 220-222°C
IR (KBr): 2939, 2806, 2783, 1460, 1392 cm^{-1}
NMR (DMSO-d_6, δ): 0.99 (1H, q, J=12.4Hz), 1.69 (1H, m), 1.90-2.25 (2H, m), 2.50 (2H, t, J=12.3Hz), 3.10-3.40 (6H, m), 3.23 (6H, s)
MASS (APCI): 174 $(M+H)^+$ (free)

(5) cis-2,6-Dimethoxymethylmorpholine hydrochloride
IR (Neat): 2935, 2819, 1595, 1513, 1456 cm^{-1}
NMR ($CDCl_3$, δ): 2.73 (2H, t, J=12.0Hz), 3.18 (2H, d, J=12.0Hz), 3.35 (6H, s), 3.35-3.46 (4H, m), 3.92-4.05 (2H, m)
MASS (APCI): 176 $(M+H)^+$ (free)

(6) 2,2-Dimethoxymethylmorpholine hydrochloride
IR (Neat): 2935, 2522, 1594, 1454 cm^{-1}
NMR ($CDCl_3$, δ): 2.92-3.00 (4H, m), 3.29 (6H, s), 3.46 (2H, d, J=10.2Hz), 3.51 (2H, d, J=10.2Hz), 3.81-3.86 (2H, m)
MASS (APCI): 176 $(M+H)^+$ (free)

(7) 8-Oxa-3-azabicyclo[3.2.1]octane hydrochloride
mp: 205-207.5°C
IR (KBr): 2920, 2792, 1591, 1442 cm^{-1}
NMR (DMSO-d_6, δ): 1.85-2.18 (4H, m), 2.97-3.08 (4H, m), 4.39-4.40 (2H, m)
MASS (APCI): 114 $(M+H)^+$ (free)

Preparation 127

The following compounds were obtained according to a similar manner to that of Preparation 89.

(1) (2S,4R)-1-(2-Hydroxyethyl)-4-methoxy-2-(methoxymethyl)-pyrrolidine
IR (Neat): 3400, 2881, 1660, 1458, 1379 cm^{-1}
NMR ($CDCl_3$, δ): 1.77 (1H, m), 2.00 (1H, m), 2.45 (1H, dd, J=10.4, 4.5Hz), 2.62 (1H, dt, J=12.7, 3.7Hz), 2.95-3.11 (2H, m), 3.29-3.45 (3H, m), 3.30 (3H, s), 3.36 (3H, s), 3.50-3.70 (2H, m), 3.90 (1H, m)
MASS (APCI): 190 $(M+H)^+$

(2) 2,2-Dimethyl-4-(2-hydroxyethyl)morpholine
IR (Neat): 2972, 2941, 1458, 1387 cm^{-1}
NMR ($CDCl_3$, δ): 1.26 (6H, s), 2.31 (2H, s), 2.45-2.54 (4H, m), 3.63 (2H, t, J=5.1Hz), 3.77 (2H, t, J=5.1Hz)
MASS (APCI): 160 $(M+H)^+$

(3) (3S,4S)-1-(2-Bromoethyl)-3,4-dimethoxypyrrolidine hydrochloride

Preparation 128

The following compounds were obtained according to a similar manner to that of Preparation 90.

(1) (2S,4R)-1-(2-Chloroethyl)-4-methoxy-2-(methoxymethyl)-pyrrolidine hydrochloride
IR (Neat): 3400, 2939, 1645, 1450 cm^{-1}
NMR (DMSO-d_6, δ): 1.80 (1H, m), 2.23 (1H, m), 3.26 (3H, s), 3.32 (3H, s), 3.20-4.20 (10H, m)
MASS (APCI): 208 $(M+H)^+$ (free)

(2) 2,2-Dimethyl-4-(2-chloroethyl)morpholine hydrochloride

mp: 180-185°C

IR (KBr): 2978, 2677, 2630, 2584, 1456 cm^{-1}

NMR (DMSO-d_6, δ): 1.18 (3H, s), 1.44 (3H, s), 2.80-3.10 (2H, m), 3.30-3.91 (6H, m), 4.10 (2H, t, J=6.9Hz)

MASS (APCI): 178 $(M+H)^+$ (free)

(3) (3S,4S)-1-(2-Chloroethyl)-3,4-dimethoxypyrrolidine hydrochloride

IR (Neat): 3400, 2563, 2440, 1637, 1460, 1113 cm^{-1}

NMR (DMSO-d_6, δ): 3.20-3.86 (6H, m), 3.32 (6H, s), 3.92-4.16 (4H, m), 11.44 (1H, s)

MASS (APCI): 194 $(M+H)^+$ (free)

Preparation 129

A solution of 3-dimethylamino-1H-pyrrolo[3,2-b]pyridine (1.53 g) and hexamethylenetetramine (1.22 g) in 6.68 g of 66% propionic acid was added dropwise to a refluxing solution of 2.44 g of hexamethylenetetramine in 8.92 g of the same solvent. The addition was carried out over a period of one hour and the solution was refluxed 3.5 hours more. The solution was concentrated in vacuo and thereto water (30 ml), ethyl acetate (25 ml), and tetrahydrofuran (20 ml) were added. The organic layer was separated, dried over sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel (12 g) using a mixed solvent of dichloromethane and methanol (15:1). The fractions containing the objective compound were collected and evaporated under reduced pressure to give a powder of 3-formyl-1H-pyrrolo[3,2-b]pyridine (0.45 g).

mp: 230°C (decomp.)

IR (KBr): 2744, 1658, 1466, 1408, 1142, 1113, 777 cm^{-1}

NMR (DMSO-d_6, δ): 7.27 (1H, dd, J=4.6 and 8.3Hz), 7.92 (1H, d, J=8.3Hz), 8.44 (1H, s), 8.50 (1H, d, J=4.6Hz), 10.19 (1H, s), 12.38 (1H, s)

MASS (APCI): 147 $(M+H)^+$

Preparation 130

The following compounds were obtained according to a similar manner to that of Preparation 125.

(1) (3S,4S)-1-(tert-Butoxycarbonyl)-3,4-dimethoxypyrrolidine
IR (Neat): 1690, 1410, 1365, 1165, 1100 cm^{-1}
NMR ($CDCl_3$, δ): 1.45 (9H, s), 3.37 (6H, s), 3.30-3.56 (4H, m), 3.72-3.85 (2H, m)
MASS (APCI): 132 $(M-Boc+H)^+$

(2) cis-2,6-Dimethoxymethyl-1-benzylpiperidine
IR (Neat): 2924, 2883, 1489, 1450 cm^{-1}
NMR ($CDCl_3$, δ): 1.30-1.85 (6H, m), 2.68-2.78 (2H, m), 3.13 (6H, s), 3.18 (2H, dd, J=9.6, 6.2Hz), 3.35 (2H, dd, J=9.6, 4.4Hz), 3.84 (2H, s), 7.17-7.42 (5H, m)
MASS (APCI): 264 $(M+H)^+$

(3) cis-3,5-Dimethoxymethyl-1-benzylpiperidine
IR (Neat): 2920, 2829, 1454, 1389 cm^{-1}
NMR ($CDCl_3$, δ): 0.68 (1H, q, J=12.2Hz), 1.61 (2H, t, J=11.1Hz), 1.78 (1H, m), 1.85-2.20 (2H, m), 2.90-3.05 (2H, m), 3.19 (4H, d, J=6.2Hz), 3.29 (6H, s), 3.52 (2H, s), 7.20-7.32 (5H, m)
MASS (APCI): 264 $(M+H)^+$

Preparation 131

A solution of (S)-methyl glycidyl ether (10 g) and benzylamine (3.62 g) in methanol (50 ml) was stirred at 55°C for 2 hours. To the mixture was added (S)-methyl glycidyl ether (1 g), and the mixture was stirred at 55°C for 2 hours, and then evaporated under reduced pressure. Toluene was added to the residue and evaporated under reduced pressure to

give (2S)-1-[N-benzyl-N-[(2S)-2-hydroxy-3-methoxypropyl]amino]-3-methoxypropan-2-ol (8.84 g) as a pale yellow oil.

IR (Neat): 3430, 3402, 2889, 1454 cm^{-1}

NMR ($CDCl_3$, δ): 2.52-2.70 (4H, m), 3.34 (6H, s), 3.26-3.44 (4H, m), 3.61 (1H, d, J=13.7Hz), 3.81-3.92 (2H, m), 3.84 (1H, d, J=13.7Hz), 7.20-7.33 (5H, m)

MASS (APCI): 284 $(M+H)^+$

Preparation 132

A mixture of triphenylphosphine (10.2 g), diethyl azodicarboxylate (6.12 ml), and (2S)-1-[N-benzyl-N-[(2S)-2-hydroxy-3-methoxypropyl]amino]-3-methoxypropan-2-ol (7.34 g) in tetrahydrofuran (70 ml) was stirred at 0°C for 5 hours. To the mixture was added successively triphenylphosphine (2.04 g) and diethyl azodicarboxylate (1.2 ml), and the mixture was stirred at 0°C for 3 hours. The mixture was poured into water and extracted with dichloromethane (x3). The combined extracts were washed with brine, dried over sodium sulfate, and evaporated. Isopropyl ether (50 ml) was added to the residue and stirred at room temperature for 30 minutes. The insoluble precipitate was filtered off, and the solution was evaporated and purified twice with column chromatography (1st: silica gel 800 ml, ethyl acetate:isopropyl ether = 2:8 - 3:7) (2nd: silica gel 300 ml, ethyl acetate:isopropyl ether = 3:97 - 10.90) to give 4-benzyl-cis-2,6-dimethoxymethylmorpholine (2.65 g) as an oil.

IR (Neat): 2883, 1514, 1458, 1099 cm^{-1}

NMR ($CDCl_3$, δ): 1.93 (2H, t, J=11.0Hz), 2.77 (2H, d, J=11.0Hz), 3.34 (6H, s), 3.36-3.50 (4H, m), 3.51 (2H, s), 3.75-3.87 (2H, m), 7.25-7.32 (5H, m)

MASS (APCI): 266 $(M+H)^+$

Preparation 133

To a solution of N-benzylethanolamine (302 g) in a

mixture of water (8.92 ml) and toluene (1510 ml) and diglyme (151 ml) was added dropwise sulfuric acid (128 ml) over 30 minutes, and the mixture was stirred under reflux for 6 hours. After cooled to room temperature, to the mixture was added methanol (300 ml), and then the mixture was stirred for 1 hour. The precipitate was filtered and washed with methanol (300 ml x 4), and dried to give 2-(N-benzylamino)ethyl hydrogen sulfate (352.6 g) as a white powder.

MASS (APCI): 232 $(M+H)^+$

Elemental Analysis Calcd. for $C_9H_{13}N_1O_4S$:

Calcd. C: 46.74%, H: 5.67%, N: 6.06%

Found. C: 46.42%, H: 5.63%, N: 5.93%

Preparation 134

To a solution of 2-(N-benzylamino)ethyl hydrogen sulfate (28 g) in a mixture of water (36.3 ml) and 40% sodium hydroxide aqueous solution (12.1 ml) was added 2,2-bis(methoxymethyl)oxirane (16.0 g) at room temperature over 30 minutes. After stirring at room temperature for 87 hours, 40% sodium hydroxide aqueous solution (73 ml) was added dropwise to the mixture over 20 minutes. The mixture was stirred at room temperature for 1 hour and at 40°C for 20 hours, and extracted with ethyl acetate (100 ml x 3). The organic layer was extracted with 1N hydrochloric acid (x 6). The combined extracts were neutralized with sodium hydroxide, and then added sodium chloride, and extracted with ethyl acetate (100 ml x 3). The combined extracts were washed with brine, dried over magnesium sulfate, and evaporated under reduced pressure to give 4-benzyl-2,2-dimethoxymethylmorpholine (31.79 g) as an orange oil.

IR (Neat): 2922, 2877, 2812, 1454 cm^{-1}

NMR ($CDCl_3$, δ): 2.38-2.44 (4H, m), 3.27-3.45 (4H, m), 3.37 (6H, s), 3.65 (2H, d, J=9.6Hz), 3.77-3.84 (2H, m), 7.20-7.34 (5H, m)

MASS (APCI): 266 $(M+H)^+$

Preparation 135

A mixture of 2,5-bis(hydroxymethyl)tetrahydrofuran bis(p-toluenesulfonate) (10 g) and benzylamine (9.7 g) was stirred at 70°C for 24 hours. To the mixture was added a solution of sodium hydroxide (1.85 g) in methanol (30 ml). After stirring at room temperature for 30 minutes, the mixture was filtered. The filtrate was evaporated, added dichloromethane, and filtered. The filtrate was evaporated under reduced pressure, and purified with column chromatography (silica gel, 250 ml, ethyl acetate:hexane = 1:4) to give 3-benzyl-8-oxa-3-azabicyclo[3.2.1]octane (4.05 g) as an oil.

IR (Neat): 2951, 2800, 1452 cm^{-1}

NMR ($CDCl_3$, δ): 1.78-2.07 (4H, m), 2.33 (2H, dd, J=11.1 and 1.8Hz), 2.54 (2H, br d, J=11.1Hz), 3.45 (2H, s), 4.25-4.28 (2H, m), 7.18-7.34 (5H, m)

MASS (APCI): 204 $(M+H)^+$

Example 38

(1) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-(2,2-dimethylmorpholino)ethyl]-2-[4-(trifluoromethyl)benzyl]-piperazine dihydrochloride

$[\alpha]_D^{26}$: +11.00° (C=0.25, MeOH)

mp: 215-231°C

IR (KBr): 3438, 1645, 1329, 1281 cm^{-1}

NMR (DMSO-d_6, δ): 1.25, 1.33 (6H, s), 2.60-5.30 (19H, m), 7.21-8.19 (7H, m)

MASS (APCI): 626 $(M+H)^+$ (free)

(2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-[(2S,5S)-2-methoxymethyl-5-methylmorpholino]ethyl]-2-[4-(trifluoromethyl)benzyl]piperazine dihydrochloride

$[\alpha]_D^{26}$: +12.33° (C=0.25, MeOH)

mp: 142-182°C
IR (KBr): 1647, 1281 cm^{-1}
NMR (DMSO-d_6, δ): 1.16 (3H, d, J=6.2Hz), 2.70-5.30 (24H, m), 7.21-8.19 (7H, m)
MASS (APCI): 656 $(M+H)^+$ (free)

(3) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-(cis-2,6-dimethoxymethylmorpholino)ethyl]-2-[4-(trifluoromethyl)-benzyl]piperazine dihydrochloride
$[\alpha]_D^{24}$: +9.00° (C=0.25, MeOH)
mp: 130-138°C
IR (KBr): 3437, 1647, 1427, 1329, 1282 cm^{-1}
NMR (DMSO-d_6, δ): 2.80-5.30 (29H, m), 7.21-8.18 (7H, m)
MASS (APCI): 686 $(M+H)^+$ (free)

(4) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-(2,2-dimethoxymethylmorpholino)ethyl]-2-[4-(trifluoromethyl)-benzyl]piperazine dihydrochloride
$[\alpha]_D^{26}$: +5.27° (C=0.25, MeOH)
mp: 123-149°C
IR (KBr): 3435, 1647 cm^{-1}
NMR (DMSO-d_6, δ): 2.70-5.30 (29H, m), 7.21-8.19 (7H, m)
MASS (APCI): 686 $(M+H)^+$ (free)

(5) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)ethyl]-2-[4-(trifluoromethyl)benzyl]piperazine dihydrochloride
$[\alpha]_D^{25}$: +11.67° (C=0.25, MeOH)
mp: 232-250°C
IR (KBr): 3438, 1645, 1281 cm^{-1}
NMR (DMSO-d_6, δ): 1.91-2.27 (4H, m), 2.80-5.40 (19H, m), 7.21-8.19 (7H, m)
MASS (APCI): 624 $(M+H)^+$ (free)

(6) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-(2,2-

dimethylmorpholino)ethyl]-2-(4-fluoro-3-methoxybenzyl)piperazine dihydrochloride
$[\alpha]_D^{26}$: +9.73° (C=0.25, MeOH)
mp: 152-162°C
IR (KBr): 3438, 1645, 1516, 1282 cm^{-1}
NMR (DMSO-d_6, δ): 1.30 (6H, br s), 2.60-5.30 (22H, m), 6.40-8.20 (6H, m)
MASS (APCI): 606 $(M+H)^+$ (free)

(7) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-[(2S,5S)-2-methoxymethyl-5-methylmorpholino]ethyl]-2-(4-fluoro-3-methoxybenzyl)piperazine dihydrochloride
$[\alpha]_D^{24}$: +12.33° (C=0.25, MeOH)
mp: 140-164°C
IR (KBr): 3437, 1645, 1282 cm^{-1}
NMR (DMSO-d_6, δ): 1.16 (3H, d, J=6.1Hz), 2.70-5.30 (27H, m), 6.50-8.20 (6H, m)
MASS (APCI): 636 $(M+H)^+$ (free)

(8) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]]-4-[2-(cis-2,6-dimethoxymethylmorpholino)ethyl]-2-(4-fluoro-3-methoxybenzyl)piperazine dihydrochloride
$[\alpha]_D^{26}$: +10.60° (C=0.25, MeOH)
mp: 148-156°C
IR (KBr): 1645, 1516, 1281 cm^{-1}
NMR (DMSO-d_6, δ): 2.60-5.20 (32H, m), 6.40-8.20 (6H, m)
MASS (APCI): 666 $(M+H)^+$ (free)

(9) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-(2,2-dimethoxymethylmorpholino)ethyl]-2-(4-fluoro-3-methoxybenzyl)pipeazine dihydrochloride
$[\alpha]_D^{23}$: +6.60° (C=0.25, MeOH)
mp: 132-150°C
IR (KBr): 3437, 1645, 1516, 1282 cm^{-1}
NMR (DMSO-d_6, δ): 2.60-5.30 (32H, m), 6.45-8.20 (6H, m)

MASS (APCI): 666 $(M+H)^+$ (free)

(10) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-(8-oxa-3-azabicyclo[3.2.1]octan-3-yl)ethyl]-2-(4-fluoro-3-methoxybenzyl)piperazine dihydrochloride
$[\alpha]_D^{23}$: +13.20° (C=0.25, MeOH)
mp: 163-178°C
IR (KBr): 3431, 1645, 1518, 1427, 1282 cm^{-1}
NMR (DMSO-d_6, δ): 1.91-2.30 (4H, m), 2.70-5.30 (22H, m), 6.45-8.25 (6H, m)
MASS (APCI): 604 $(M+H)^+$ (free)

Example 39

The following compounds were obtained according to a similar manner to that of Example 1 using N,N-diisopropylethylamine instead of potassium carbonate as a base.

(1) 4-[[(2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]piperazin-2-yl]-methyl]-2-(tert-butyldimethylsilyloxy)benzoic acid methyl ester
IR (Neat): 1677, 1643, 1438, 1280 cm^{-1}
NMR ($CDCl_3$, δ): 0.10-0.30 (6H, m), 0.99 (9H, s), 2.00-5.10 (22H, m), 3.38 (3H, s), 3.87 (3H, s), 6.30-7.90 (6H, m)
MASS (APCI): 784 $(M+Na)^+$, 763 $(M+H)^+$

(2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-methoxybenzyl)-4-[2-[(2S)-2-(methoxymethyl)morpholino]-ethyl]piperazine dihydrochloride
$[\alpha]_D^{25}$: -5.16° (C=0.32, MeOH)
mp: 146-149°C
IR (KBr): 1645, 1282, 1182, 1136 cm^{-1}
NMR (DMSO-d_6, δ): 2.60-5.20 (28H, m), 6.75-6.90 (4H, m),

7.29-8.21 (3H, m)
MASS (APCI): 604 $(M+H)^+$ (free)

(3) (2R)-2-[3-(tert-Butyldimethylsilyloxy)-4-methylbenzyl]-1-[3-methoxy-5-(trifluoromethyl)benzoyl]-4-[2-(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)ethyl]piperazine
IR (Neat): 2935, 1641, 1464, 1421 cm^{-1}
NMR ($CDCl_3$, δ): 0.13 (6H, br s), 0.99 (9H, s), 2.15 (3H, s), 2.10-5.10 (19H, m), 3.81 (3H, s), 6.20-7.10 (7H, m), 7.32 (1H, d, J=6.7Hz), 8.40 (1H, d, J=3.8Hz)
MASS (APCI): 683 $(M+H)^+$

(4) (2R)-2-[3-(tert-Butyldimethylsilyloxy)-4-methylbenzyl]-4-[4-(3,3-dimethylmorpholino)-2-butynyl]-1-[3-methoxy-5-(trifluoromethyl)benzoyl]piperazine

IR (Neat): 2952, 1645, 1510 cm^{-1}
NMR ($CDCl_3$, δ): 0.14 (6H, br s), 0.99 (9H, s), 1.05 (6H, s), 2.15 (3H, s), 2.20-5.20 (19H, m), 3.81 (3H, s), 6.20-7.58 (6H, m)
MASS (APCI): 688 $(M+H)^+$

(5) (2R)-1-[3-(Dimethylsulfamoyl)-5-(trifluoromethyl)-benzoyl]-4-[2-(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)ethyl]-2-[4-(trifluoromethyl)benzyl]piperazine trihydrochloride
$[\alpha]_D^{26}$: +1.33° (C=0.25, MeOH)
mp: 190-194°C
IR (KBr): 3398, 1647 cm^{-1}
NMR (DMSO-d_6, δ): 2.66 (6H, s), 2.80-5.30 (19H, m), 6.90-8.71 (10H, m)
MASS (APCI): 684 $(M+H)^+$ (free)

(6) (2R)-1-[3-Methylsulfonyl-5-(trifluoromethyl)benzoyl]-2-

[4-(trifluoromethyl)benzyl]-4-[2-(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)ethyl]piperazine trihydrochloride
$[\alpha]_D^{26}$: -2.33° (C=0.25, MeOH)
mp: 192-197°C
IR (KBr): 3433, 3400, 1647 cm^{-1}
NMR (DMSO-d_6, δ): 2.70-5.30 (22H, m), 7.05-8.68 (10H, m)
MASS (APCI): 655 $(M+H)^+$ (free)

(7) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-[(2R)-2-(methoxymethyl)morpholino]ethyl]-2-[4-(trifluoromethyl)-benzyl]piperazine dihydrochloride
$[\alpha]_D^{26.5}$: +5.18° (C=0.28, MeOH)
mp: 188-194°C
IR (KBr): 3438, 1645, 1516, 1464, 1456 cm^{-1}
NMR (DMSO-d_6, δ): 2.50-5.30 (22H, m), 3.27 (3H, s), 7.10-8.30 (7H, m)
MASS (API-ES positive): 642 $(M+H)^+$ (free)

(8) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-[(2S,4R)-4-methoxy-2-(methoxymethyl)pyrrolidino]ethyl]-2-[4-(trifluoromethyl)benzyl]piperazine dihydrochloride
$[\alpha]_D^{26.7}$: -17.43° (C=0.23, MeOH)
mp: 56.59°C
IR (KBr): 3438, 1647, 1427 cm^{-1}
NMR (DMSO-d_6, δ): 1.70-5.40 (21H, m), 3.29 (3H, s), 3.35 (3H, s), 7.10-7.80 (6H, m), 8.19 (1H, br s)
MASS (APCI): 656 $(M+H)^+$ (free)

(9) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-[(3S,4S)-3,4-dimethoxypyrrolidino]ethyl]-2-[4-(trifluoromethyl)-benzyl]piperazine dihydrochloride
$[\alpha]_D^{23.1}$: +5.94° (C=0.202, MeOH)
mp: 203-208°C
IR (KBr): 3437, 2565, 2440, 1647, 1429, 1331, 1282, 1178, 1128, 1066 cm^{-1}

NMR (DMSO-d_6, δ): 2.76-5.32 (25H, m), 7.10-8.26 (7H, m)
MASS (APCI): 642 $(M+H)^+$ (free)

(10) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-fluoro-3-methoxybenzyl)-4-[2-[(2S,4R)-4-methoxy-2-(methoxymethyl)pyrrolidino]ethyl]piperazine dihydrochloride
$[\alpha]_D^{26.6}$: -12.27° (C=0.30, MeOH)
mp: 128-134°C
IR (KBr): 3437, 3400, 1645, 1516 cm^{-1}
NMR (DMSO-d_6, δ): 1.70-5.30 (21H, m), 3.29 (3H, s), 3.35 (3H, s), 3.57 (3H, s), 6.40-8.30 (6H, m)
MASS (APCI): 636 $(M+H)^+$ (free)

(11) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-fluoro-3-methoxybenzyl)-4-[2-[(2R)-2-(methoxymethyl)morpholino]-ethyl]piperazine dihydrochloride
$[\alpha]_D^{26.8}$: +6.24° (C=0.33, MeOH)
mp: 139-148°C
IR (KBr): 3438, 1644, 1516, 1464, 1427 cm^{-1}
NMR (DMSO-d_6, δ): 2.60-5.30 (25H, m), 3.27 (3H, s), 6.40-8.30 (6H, m)
MASS (APCI): 622 $(M+H)^+$ (free)

(12) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-[(3S,4S)-3,4-dimethoxypyrrolidino]ethyl]-2-(4-fluoro-3-methoxybenzyl)piperazine dihydrochloride
$[\alpha]_D^{23.5}$: +8.05° (C=0.205, MeOH)
mp: 112-120°C
IR (KBr): 3431, 2561, 2436, 1645, 1516, 1464, 1427, 1282, 1182, 1134, 1034 cm^{-1}
NMR (DMSO-d_6, δ): 2.65-5.24 (28H, m), 6.44-8.30 (6H, m)
MASS (APCI): 622 $(M+H)^+$ (free)

(13) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-chloro-3-hydroxybenzyl)-4-[2-[(2R)-2-(methoxymethyl)morpholino]-

ethyl]piperazine dihydrochloride
$[\alpha]_D^{26.5}$: -11.28° (C=0.27, MeOH)
mp: 204-214°C
IR (KBr): 1645, 1539, 1516 cm^{-1}
NMR (DMSO-d_6, δ): 2.50-5.20 (22H, m), 3.27 (3H, s), 6.30-8.30 (6H, m), 9.90-10.30 (1H, br)
MASS (API-ES positive): 624 $(M+H)^+$ (free)

(14) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-chloro-3-hydroxybenzyl)-4-[2-[(2S,4R)-4-methoxy-2-(methoxymethyl)pyrrolidino]ethyl]piperazine dihydrochloride
$[\alpha]_D^{26.4}$: -25.54° (C=0.33, MeOH)
mp: 95-105°C
IR (KBr): 3400, 1645, 1516, 1429 cm^{-1}
NMR (DMSO-d_6, δ): 1.70-5.30 (21H, m), 3.28 (3H, s), 3.35 (3H, s), 6.20-8.30 (6H, m), 10.07-11.26 (1H, br)
MASS (APCI): 638 $(M+H)^+$ (free)

(15) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-chloro-3-hydroxybenzyl)-4-[2-[(3S,4S)-3,4-dimethoxypyrrolidino]-ethyl]piperazine dihydrochloride
$[\alpha]_D^{23.8}$: -6.49° (C=0.23, MeOH)
mp: 150-155°C
IR (KBr): 3398, 2600, 2436, 1645, 1429, 1281, 1180, 1136, 1107, 1047 cm^{-1}
NMR (DMSO-d_6, δ): 2.55-5.15 (25H, m), 6.24-8.30 (6H, m)
MASS (APCI): 624 $(M+H)^+$ (free)

(16) (2R)-2-[3-(tert-Butyldimethylsilyloxy)-4-chlorobenzyl]-1-[3-chloro-5-(trifluoromethyl)benzoyl]-4-[2-(cis-2,6-dimethylmorpholino)ethyl]piperazine
IR (Neat): 2935, 1641, 1417 cm^{-1}
NMR ($CDCl_3$, δ): 0.18 (6H, br s), 1.02 (9H, s), 1.16 (6H, d, J=6.3Hz), 1.76 (2H, t, J=10.7Hz), 2.00-5.10 (17H, m), 6.30-7.50 (5H, m), 7.61 (1H, s)

MASS (APCI): 688 $(M+H)^+$

(17) (2R)-2-[3-(tert-Butyldimethylsilyloxy)-4-chlorobenzyl]-1-[3-chloro-5-(trifluoromethyl)benzoyl]-4-[2-(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)ethyl]piperazine
IR (KBr): 2954, 2935, 1643, 1419 cm^{-1}
NMR (DMSO-d_6, δ): 0.00-0.07 (6H, br), 0.83 (9H, s), 1.70-5.00 (19H, m), 6.20-8.10 (8H, m), 8.18 (1H, d, J=4.7Hz)
MASS (API-ES positive): 707 $(M+H)^+$

Example 40

The following compound was obtained by reacting (2R)-4-(2-chloroethyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[4-(trifluoromethyl)benzyl]piperazine hydrochloride with (2S)-2-(hydroxymethyl)pyrrolidine with a reaction condition similar to that of Example 1 using N,N-diisopropylethylamine instead of potassium carbonate as a base.

(2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-[(2S)-2-(hydroxymethyl)pyrrolidino]ethyl]-2-[4-(trifluoromethyl)-benzyl]piperazine dihydrochloride
$[\alpha]_D^{24.0}$: +6.43° (C=0.28, MeOH)
mp: 221-224°C
IR (KBr): 1643, 1516, 1427 cm^{-1}
NMR (DMSO-d_6, δ): 1.65-2.30 (4H, m), 2.60-5.40 (19H, m), 7.10-8.30 (7H, m)
MASS (APCI): 612 $(M+H)^+$ (free)

Example 41

The following compounds were obtained according to a similar manner to that of Example 40.

(1) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-(cis-2,6-dihydroxymethylpiperidino)ethyl]-2-[4-(trifluoromethyl)-

benzyl]piperazine dihydrochloride
$[\alpha]_D^{24.2}$: +10.36° (C=0.14, MeOH)
mp: 164-167°C
IR (KBr): 3396, 3369, 1645, 1516, 1427 cm^{-1}
NMR (DMSO-d_6, δ): 1.30-2.10 (6H, m), 2.40-5.60 (21H, m), 7.00-8.30 (7H, m)
MASS (APCI): 656 $(M+H)^+$ (free)

(2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-(cis-2,6-dimethoxymethylpiperidino)ethyl]-2-[4-(trifluoromethyl)-benzyl]piperazine dihydrochloride
$[\alpha]_D^{23.1}$: +5.12° (C=0.21, MeOH)
mp: 147-151°C
IR (KBr): 1645, 1516, 1454, 1427 cm^{-1}
NMR (DMSO-d_6, δ): 1.40-2.00 (6H, m), 2.80-5.30 (25H, m), 7.10-8.40 (7H, m)
MASS (APCI): 684 $(M+H)^+$ (free)

(3) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-(cis-3,5-dimethoxymethylpiperidino)ethyl]-2-[4-(trifluoromethyl)-benzyl]piperazine dihydrochloride
$[\alpha]_D^{23.4}$: +8.28° (C=0.32, MeOH)
mp: 157-160°C
IR (KBr): 3438, 1647, 1464, 1427 cm^{-1}
NMR (DMSO-d_6, δ): 1.05 (1H, q, J=12.4Hz), 1.70 (1H, m), 2.10-5.40 (23H, m), 3.24 (6H, s), 7.10-8.30 (7H, m)
MASS (APCI): 684 $(M+H)^+$ (free)

(4) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-[(3S,4S)-3,4-dihydroxypyrrolidino]ethyl]-2-[4-(trifluoromethyl)-benzyl]piperazine dihydrochloride
$[\alpha]_D^{23.9}$: +7.37° (C=0.29, MeOH)
mp: 154-159°C
IR (KBr): 3398, 3369, 1645, 1427 cm^{-1}
NMR (DMSO-d_6, δ): 2.20-5.40 (21H, m), 7.1-8.3 (7H, m)

MASS (APCI): 614 $(M+H)^+$ (free)

(5) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-fluoro-3-methoxybenzyl)-4-[2-[(2S)-2-(hydroxymethyl)pyrrolidino]-ethyl]piperazine dihydrochloride
$[\alpha]_D^{24.1}$: +4.76° (C=0.25, MeOH)
mp: 198-201°C
IR (KBr): 1645, 1516, 1464, 1425 cm^{-1}
NMR (DMSO-d_6, δ): 1.60-5.40 (23H, m), 3.59 (3H, s), 6.40-8.30 (6H, m)
MASS (APCI): 592 $(M+H)^+$ (free)

(6) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-(cis-2,6-dihydroxymethylpiperidino)ethyl]-2-(4-fluoro-3-methoxybenzyl)piperazine dihydrochloride
$[\alpha]_D^{24.3}$: +11.33° (C=0.27, MeOH)
mp: 159-161°C
IR (KBr): 3367, 1645, 1516, 1464, 1427 cm^{-1}
NMR (DMSO-d_6, δ): 1.40-2.00 (6H, m), 2.60-5.30 (24H, m), 6.40-8.30 (6H, m)
MASS (APCI): 636 $(M+H)^+$ (free)

(7) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-(cis-3,5-dimethoxymethylpiperidino)ethyl]-2-(4-fluoro-3-methoxybenzyl)piperazine dihydrochloride
$[\alpha]_D^{23.7}$: +9.45° (C=0.28, MeOH)
mp: 150-156°C
IR (KBr): 3438, 2939, 1645, 1518, 1464, 1427 cm^{-1}
NMR (DMSO-d_6, δ): 1.05 (1H, q, J=12.3Hz), 1.70 (1H, m), 2.10-5.30 (26H, m), 3.24 (6H, s), 6.40-8.30 (6H, m)
MASS (APCI): 664 $(M+H)^+$ (free)

Example 42

The following compounds were obtained according to a similar manner to that of Example 13.

(1) (2R)-2-(3-Hydroxy-4-methylbenzyl)-1-[3-methoxy-5-(trifluoromethyl)benzoyl]-4-[2-(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)ethyl]piperazine trihydrochloride
$[\alpha]_D^{27}$: -17.11° (C=0.15, MeOH)
mp: 192-208°C
IR (KBr): 1643, 1628, 1464 cm^{-1}
NMR (DMSO-d_6, δ): 2.06 (3H, s), 2.60-5.10 (22H, m), 6.20-7.30 (6H, m), 7.62-7.69 (1H, m), 8.05 (1H, d, J=7.8Hz), 8.67 (1H, d, J=4.0Hz)
MASS (APCI): 569 $(M+H)^+$ (free)

(2) (2R)-4-[4-(3,3-Dimethylmorpholino)-2-butynyl]-2-(3-hydroxy-4-methylbenzyl)-1-[3-methoxy-5-(trifluoromethyl)benzoyl]piperazine dihydrochloride
$[\alpha]_D^{27}$: +13.87° (C=0.25, MeOH)
mp: 181-188°C
IR (KBr): 1645, 1464, 1425 cm^{-1}
NMR (DMSO-d_6, δ): 1.25-1.32 (6H, m), 2.07 (3H, s), 2.70-5.20 (22H, m), 6.20-7.29 (6H, m)
MASS (APCI): 574 $(M+H)^+$ (free)

(3) (2R)-2-(4-Chloro-3-hydroxybenzyl)-1-[3-chloro-5-(trifluoromethyl)benzoyl]-4-[2-(cis-2,6-dimethylmorpholino)ethyl]piperazine dihydrochloride
$[\alpha]_D^{26.5}$: -12.04° (C=0.25, MeOH)
mp: 196-199°C
IR (KBr): 3398, 1643, 1514, 1456, 1425 cm^{-1}
NMR (DMSO-d_6, δ): 1.15 (6H, d, J=6.1Hz), 2.60-5.20 (19H, m), 6.30-8.10 (6H, m), 10.08 (1H, br s)
MASS (APCI): 574 $(M+H)^+$ (free)

(4) (2R)-2-(4-Chloro-3-hydroxybenzyl)-1-[3-chloro-5-(trifluoromethyl)benzoyl]-4-[2-(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)ethyl]piperazine trihydrochloride
$[\alpha]_D^{26.5}$: -20.57° (C=0.28, MeOH)

mp: 200-204°C

IR (KBr): 3430, 3400, 1645, 1514, 1464, 1425 cm^{-1}

NMR (DMSO-d_6, δ): 2.60-5.20 (19H, m), 6.30-8.10 (8H, m), 8.63 (1H, d, J=4.6Hz), 10.09 (1H, br)

MASS (APCI): 593 $(M+H)^+$ (free)

Example 43

The following compounds were obtained according to a similar manner to that of Example 41.

(1) (2R)-2-(4-Chlorobenzyl)-4-[2-[(2S)-2-(methoxymethyl)-morpholino]ethyl]-1-[3-(4-pyridyl)-5-(trifluoromethyl)-benzoyl]piperazine trihydrochloride

$[\alpha]_D^{27}$: +1.5° (C=0.5, MeOH)

IR (KBr): 1645, 1510, 1460, 1425, 1270, 1240, 1175, 1135 cm^{-1}

NMR (DMSO-d_6, δ): 2.62-5.15 (22H, m), 3.28 (3H, s), 6.16-9.01 (11H, m)

MASS (APCI): 617 $(M)^+$ (free)

(2) (2R)-2-(4-Chlorobenzyl)-4-[2-[(2S)-2-(methoxymethyl)-morpholino]ethyl]-1-[3-methyl-5-(trifluoromethyl)-benzoyl]piperazine dihydrochloride

$[\alpha]_D^{27}$: +10.9° (C=0.5, MeOH)

mp: 148-151°C

IR (KBr): 1645, 1510, 1465, 1425, 1270, 1230 cm^{-1}

NMR (DMSO-d_6, δ): 2.33 (3H, s), 3.28 (3H, s), 2.66-5.24 (22H, m), 6.16-7.70 (7H, m)

MASS (APCI): 554 $(M)^+$ (free)

(3) (2R)-2-(4-Chlorobenzyl)-1-[3-cyclopentylsulfonyl-5-(trifluoromethyl)benzoyl]-4-[2-[(2S)-2-(methoxymethyl)-morpholino]ethyl]piperazine dihydrochloride

$[\alpha]_D^{27}$: +12.1° (C=0.5, DMF)

mp: >230°C

IR (KBr): 1650, 1465, 1425, 1335, 1305, 1235, 1135 cm^{-1}

NMR (DMSO-d_6, δ): 1.45-1.93 (9H, m), 2.80-5.20 (22H, m), 3.27 (3H, s), 6.14-8.30 (7H, m)

MASS (APCI): 672 $(M)^+$ (free)

(4) (2R)-2-(4-Chlorobenzyl)-4-[2-[(2S)-2-(methoxymethyl)-morpholino]ethyl]-1-[3-methylthio-5-(trifluoromethyl)-benzoyl]piperazine dihydrochloride

$[\alpha]_D^{27}$: +13.3° (C=0.5, MeOH)

mp: 140-146°C

IR (KBr): 1625, 1415, 1320, 1270, 1225, 1175 cm^{-1}

NMR (DMSO-d_6, δ): 2.54 (3H, s), 2.66-5.20 (22H, m), 3.27 (3H, s), 6.66-7.64 (7H, m)

MASS (APCI): 586 $(M)^+$ (free)

(5) (2R)-2-(4-Chlorobenzyl)-1-[3-chloro-5-(trifluoromethyl)-benzoyl]-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]-piperazine dihydrochloride

$[\alpha]_D^{27}$: +7.0° (C=0.5, MeOH)

mp: 148-153°C

IR (KBr): 1645, 1460, 1420, 1315, 1270, 1230, 1175 cm^{-1}

NMR (DMSO-d_6, δ): 2.66-5.20 (22H, m), 3.28 (3H, s), 6.02-8.00 (7H, m)

MASS (APCI): 574 $(M)^+$ (free)

(6) (2R)-2-(4-Chlorobenzyl)-1-[3-fluoro-5-(trifluoromethyl)-benzoyl]-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]-piperazine dihydrochloride

$[\alpha]_D^{27}$: +10.0° (C=0.5, MeOH)

mp: 199-204°C

IR (KBr): 1645, 1425, 1235, 1175, 1135 cm^{-1}

NMR (DMSO-d_6, δ): 2.70-5.16 (22H, m), 3.28 (3H, s), 6.16-7.90 (7H, m)

MASS (APCI): 558 $(M)^+$ (free)

(7) (2R)-1-[3-Methylthio-5-(trifluoromethyl)benzoyl]-2-[4-(trifluoromethyl)benzyl]-4-[2-[(2S)-2-(methoxymethyl)-morpholino]ethyl]piperazine dihydrochloride
$[\alpha]_D^{22}$: +21.93° (C=0.25, MeOH)
mp: 153-170°C
IR (KBr): 3433, 1645 cm^{-1}
NMR (DMSO-d_6, δ): 2.54 (3H, s), 2.70-5.30 (25H, m), 6.50-7.80 (7H, m)
MASS (APCI): 620 $(M+H)^+$ (free)

(8) (2R)-1-[3-Chloro-5-(trifluoromethyl)benzoyl]-2-[4-(trifluoromethyl)benzyl]-4-[2-[(2S)-2-(methoxymethyl)-morpholino]ethyl]piperazine dihydrochloride
$[\alpha]_D^{22}$: +29.60° (C=0.21, MeOH)
mp: 168-173°C
IR (KBr): 3433, 1647 cm^{-1}
NMR (DMSO-d_6, δ): 2.80-5.30 (25H, m), 6.87-8.00 (7H, m)
MASS (APCI): 608 $(M+H)^+$ (free)

(9) (2R)-1-[3-Fluoro-5-(trifluoromethyl)benzoyl]-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]-2-[4-(trifluoromethyl)benzyl]piperazine dihydrochloride
$[\alpha]_D^{27}$: +17.47° (C=0.25, MeOH)
mp: 173-176°C
IR (KBr): 1647 cm^{-1}
NMR (DMSO-d_6, δ): 2.80-5.30 (25H, m), 6.70-7.90 (7H, m)
MASS (APCI): 592 $(M+H)^+$ (free)

(10) (2R)-4-[2-[(2S)-2-(Methoxymethyl)morpholino]ethyl]-1-[3-(4-pyridyl)-5-(trifluoromethyl)benzoyl]-2-[4-(trifluoromethyl)benzyl]piperazine trihydrochloride
$[\alpha]_D^{26}$: +13.60° (C=0.25, MeOH)
mp: 81-91°C
IR (KBr): 3435, 1643 cm^{-1}
NMR (DMSO-d_6, δ): 2.80-5.30 (25H, m), 6.88-8.98 (11H, m)

MASS (APCI): 651 $(M+H)^+$ (free)

(11) (2R)-4-[2-(cis-2,6-Dimethylmorpholino)ethyl]-1-[3-methylthio-5-(trifluoromethyl)benzoyl]-2-[4-(trifluoromethyl)benzyl]piperazine dihydrochloride
$[\alpha]_D^{27}$: +19.00° (C=0.25, MeOH)
mp: 154-156°C
IR (KBr): 3435, 1647 cm^{-1}
NMR (DMSO-d_6, δ): 1.15 (6H, d, J=6.1Hz), 2.54 (3H, s), 2.60-5.30 (19H, m), 6.50-7.70 (7H, m)
MASS (APCI): 604 $(M+H)^+$ (free)

(12) (2R)-4-[2-(cis-2,6-Dimethylmorpholino)ethyl]-1-[3-methylsulfonyl-5-(trifluoromethyl)benzoyl]-2-[4-(trifluoromethyl)benzyl]piperazine dihydrochloride
$[\alpha]_D^{25}$: +12.60° (C=0.25, MeOH)
mp: 188-195°C
IR (KBr): 1647 cm^{-1}
NMR (DMSO-d_6, δ): 1.15 (6H, d, J=6.1Hz), 2.60-5.30 (22H, m), 7.00-8.32 (7H, m)
MASS (APCI): 636 $(M+H)^+$ (free)

(13) (2R)-4-[2-(cis-2,6-Dimethylmorpholino)ethyl]-1-[3-(4-pyridyl)-5-(trifluoromethyl)benzoyl]-2-[4-(trifluoromethyl)benzyl]piperazine trihydrochloride
$[\alpha]_D^{26}$: +8.40° (C=0.25, MeOH)
mp: 135-145°C
IR (KBr): 3433, 3402, 1641 cm^{-1}
NMR (DMSO-d_6, δ): 1.15 (6H, d, J=6.2Hz), 2.60-5.30 (19H, m), 6.80-9.02 (11H, m)
MASS (APCI): 635 $(M+H)^+$ (free)

(14) (2R)-1-[3-Methylthio-5-(trifluoromethyl)benzoyl]-4-[2-(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)ethyl]-2-[4-(trifluoromethyl)benzyl]piperazine dihydrochloride

$[\alpha]_D^{27}$: +1.53° (C=0.25, MeOH)
mp: 190-210°C
IR (KBr): 3431, 1643 cm^{-1}
NMR (DMSO-d_6, δ): 2.54 (3H, s), 2.80-5.30 (19H, m), 6.50-8.71 (10H, m)
MASS (APCI): 623 $(M+H)^+$ (free)

(15) (2R)-1-[3-(4-Pyridyl)-5-(trifluoromethyl)benzoyl]-4-[2-(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)ethyl]-2-[4-(trifluoromethyl)benzyl]piperazine tetrahydrochloride
$[\alpha]_D^{26}$: -5.73° (C=0.25, MeOH)
mp: 205-218°C
IR (KBr): 3400, 1641 cm^{-1}
NMR (DMSO-d_6, δ): 2.60-5.30 (19H, m), 6.85-9.02 (14H, m)
MASS (APCI): 654 $(M+H)^+$ (free)

(16) (2R)-2-(4-Fluoro-3-methoxybenzyl)-4-[2-(cis-2,6-dimethylmorpholino)ethyl]-1-[3-methylthio-5-(trifluoromethyl)benzoyl]piperazine dihydrochloride
$[\alpha]_D^{27.3}$: +23.47° (C=0.36, MeOH)
mp: 62.5-82.4°C
IR (KBr): 1645, 1518, 1421, 1176, 1126 cm^{-1}
NMR (DMSO-d_6, δ): 1.15 (6H, d, J=6.1Hz), 2.60-4.20 (27H, m), 6.50-7.56 (6H, m)
MASS: 584 $(M+H)^+$ (free)

(17) (2R)-2-(4-Fluoro-3-methoxybenzyl)-4-[2-(cis-2,6-dimethylmorpholino)ethyl]-1-[3-(4-pyridyl)-5-(trifluoromethyl)benzoyl]piperazine trihydrochloride
$[\alpha]_D^{27.4}$: +14.30° (C=0.37, MeOH)
mp: 137.6-142.5°C
IR (KBr): 1641, 1515, 1425, 1270, 1176, 1145, 1132 cm^{-1}
NMR (DMSO-d_6, δ): 1.14 (6H, d, J=6.0Hz), 2.60-4.20 (25H, m), 6.52-8.90 (10H, m)
MASS (APCI): 615 $(M+H)^+$ (free)

(18) (2R)-2-(4-Fluoro-3-methoxybenzyl)-1-[3-methylthio-5-(trifluoromethyl)benzoyl]-4-[2-(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)ethyl]piperazine trihydrochloride
$[\alpha]_D^{27.4}$: -3.51° (C=0.39, MeOH)
mp: 143.3-147.5°C
IR (KBr): 1645, 1516, 1417, 1173, 1126 cm^{-1}
NMR (DMSO-d_6, δ): 3.80-5.20 (28H, m), 6.53-8.68 (9H, m)
MASS (APCI): 603 $(M+H)^+$ (free)

(19) (2R)-2-(4-Fluoro-3-methoxybenzyl)-1-[3-(4-pyridyl)-5-(trifluoromethyl)benzoyl]-4-[2-(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)ethyl]piperazine tetrahydrochloride
$[\alpha]_D^{27.9}$: -9.07° (C=0.46, MeOH)
mp: 236.8-248.5°C
IR (KBr): 1641, 1635, 1516, 1423, 1273, 1130 cm^{-1}
NMR (DMSO-d_6, δ): 2.65-5.10 (26H, m), 6.51-9.00 (13H, m)
MASS: 634 $(M+H)^+$ (free)

(20) (2R)-2-(4-Fluoro-3-methoxybenzyl)-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]-1-[3-(4-pyridyl)-5-(trifluoromethyl)benzoyl]piperazine trihydrochloride
$[\alpha]_D^{28}$: +32.5° (C=0.5, MeOH)
IR (KBr): 1645, 1515, 1425, 1270, 1235 cm^{-1}
NMR (DMSO-d_6, δ): 2.66-5.24 (25H, m), 3.27 (3H, s), 6.45-8.93 (10H, m)
MASS (APCI): 631 $(M+H)^+$ (free)

(21) (2R)-1-[3-Chloro-5-(trifluoromethyl)benzoyl]-2-(4-fluoro-3-methoxybenzyl)-4-[2-[(2S)-2-(methoxymethyl)-morpholino]ethyl]piperazine dihydrochloride
$[\alpha]_D^{28}$: +25.4° (C=0.5, MeOH)
mp: 139-142°C
IR (KBr): 1645, 1515, 1460, 1420, 1315, 1270, 1230 cm^{-1}
NMR (DMSO-d_6, δ): 2.72-5.21 (22H, m), 3.29 (3H, s), 3.44 (3H, s), 6.17-8.00 (6H, m)

MASS (APCI): 588 $(M)^+$ (free)

(22) (2R)-2-(4-Fluoro-3-methoxybenzyl)-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]-1-[3-methylthio-5-(trifluoromethyl)benzoyl]piperazine dihydrochloride
$[\alpha]_D^{28}$: +28.1° (C=0.5, MeOH)
mp: 132-135°C
IR (KBr): 1645, 1515, 1460, 1420, 1315, 1270, 1230, 1130 cm^{-1}
NMR (DMSO-d_6, δ): 2.54 (3H, s), 2.73-5.27 (22H, m), 3.28 (3H, s), 3.41 (3H, s), 6.15-7.83 (6H, m)
MASS (APCI): 600 $(M+H)^+$ (free)

(23) (2R)-2-(4-Fluoro-3-methoxybenzyl)-1-[3-fluoro-5-(trifluoromethyl)benzoyl]-4-[2-[(2S)-2-(methoxymethyl)-morpholino]ethyl]piperazine dihydrochloride
$[\alpha]_D^{27}$: +21.4° (C=0.5, MeOH)
IR (KBr): 1640, 1515, 1465, 1425, 1345, 1275, 1230, 1135 cm^{-1}
NMR (DMSO-d_6, δ): 2.76-5.20 (22H, m), 3.29 (3H, s), 3.42 (3H, s), 6.16-7.86 (6H, m)
MASS (APCI): 572 $(M+H)^+$ (free)

Example 44

The following compounds were obtained according to a similar manner to that of the second half of Preparation 21.

(1) (2R)-2-(4-Chloro-3-hydroxybenzyl)-1-[3-chloro-5-(trifluoromethyl)benzoyl]-4-[2-[(2S)-2-(methoxymethyl)-morpholino]ethyl]piperazine dihydrochloride
$[\alpha]_D^{28}$: +6.1° (C=0.5, MeOH)
IR (KBr): 1645, 1510, 1425, 1235, 1175 cm^{-1}
NMR (DMSO-d_6, δ): 2.55-5.10 (22H, m), 3.27 (3H, s), 6.31-8.03 (6H, m), 10.07 (1H, br s)
MASS (APCI): 590 $(M)^+$ (free)

(2) (2R)-2-(4-Chloro-3-hydroxybenzyl)-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]-1-[3-methylthio-5-(trifluoromethyl)benzoyl]piperazine dihydrochloride
$[\alpha]_D^{28}$: +15.0° (C=0.5, MeOH)
mp: 169-174°C
IR (KBr): 3475, 3420, 1640, 1425, 1320, 1270, 1230, 1135 cm^{-1}
NMR (DMSO-d_6, δ): 2.54 (3H, s), 2.56-5.10 (22H, m), 3.27 (3H, s), 6.29-7.69 (6H, m), 10.10 (1H, br s)
MASS (APCI): 602 $(M)^+$ (free)

(3) (2R)-2-(4-Chloro-3-hydroxybenzyl)-1-[3-fluoro-5-(trifluoromethyl)benzoyl]-4-[2-[(2S)-2-(methoxymethyl)-morpholino]ethyl]piperazine dihydrochloride
$[\alpha]_D^{27}$: +7.6° (C=0.5, MeOH)
mp: 176-178°C
IR (KBr): 1645, 1510, 1460, 1425, 1235, 1175 cm^{-1}
NMR (DMSO-d_6, δ): 2.52-4.98 (22H, m), 3.28 (3H, s), 6.34-7.77 (7H, m)
MASS (APCI): 574 $(M)^+$ (free)

Example 45

The following compounds were obtained according to a similar manner to that of Example 11.

(1) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-chloro-3-hydroxybenzyl)-4-[(1H-pyrrolo[3,2-b]pyridin-3-yl)-methyl]piperazine dihydrochloride
$[\alpha]_D^{25.0}$: +5.42° (C=0.60, MeOH)
mp: 208-211°C
IR (KBr): 1647, 1281, 1180, 1138 cm^{-1}
NMR (DMSO-d_6, δ): 2.60-5.10 (11H, m), 6.26-7.20 (3H, m), 7.43-7.82 (3H, m), 8.18-8.72 (4H, m), 10.08 (1H, br), 13.11 (1H, s)
MASS (APCI): 597 $(M+H)^+$ (free)

(2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-chloro-3-hydroxybenzyl)-4-[(1H-pyrrolo[2,3-b]pyridin-3-yl)-methyl]piperazine dihydrochloride

$[\alpha]_D^{24.9}$: -0.90° (C=0.50, MeOH)

mp: 197-200°C

IR (KBr): 1647, 1281, 1180, 1136 cm^{-1}

NMR (DMSO-d_6, δ): 2.60-5.20 (11H, m), 6.24-7.40 (4H, m), 7.45 (1H, s), 7.76 (1H, s), 7.95-8.55 (4H, m), 11.60 (1H, br), 12.45 (1H, s)

MASS (APCI): 597 $(M+H)^+$ (free)

Example 46

1M Methylmagnesium iodide in diethyl ether solution (3.15 ml) was added to a solution of 4-[[(2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[2-[(2S)-2-(methoxymethyl)-morpholino]ethyl]piperazin-2-yl]methyl]-2-(tert-butyldimethylsilyloxy)benzoic acid methyl ester (0.8 g) in toluene (8 ml). After being stirred at 45°C for 4 hours, the mixture was quenched with saturated aqueous ammonium chloride solution and the whole was extracted with ethyl acetate. The organic layer was separated, washed with water and brine successively, dried over magnesium sulfate, and evaporated under reduced pressure to give crude oil. The oil was purified by column chromatography on silica gel using a mixed solvent of dichloromethane and methanol (40:1) to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-(tert-butyldimethylsilyloxy)-4-(1-hydroxy-1-methylethyl)benzyl]-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]piperazine (0.333 g)

IR (Neat): 1643, 1438, 1280 cm^{-1}

NMR ($CDCl_3$, δ): 0.10-0.50 (6H, m), 1.03 (9H, s), 1.58 (6H, s), 2.00-5.10 (22H, m), 3.38 (3H, s), 6.30-7.90 (6H, m)

MASS (API-ES): 784 $(M+Na)^+$, 763 $(M+H)^+$

Example 47

Methanesulfonyl chloride (0.115 ml) was added to an ice-cooled solution of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-(tert-butyldimethylsilyloxy)-4-(1-hydroxy-1-methylethyl)benzyl]-4-[2-[(2S)-2-(methoxymethyl)morpholino]-ethyl]piperazine (0.76 g) and triethylamine (0.35 ml) in dichloromethane (9 ml). After being stirred at the same temperature for 2 hours, the mixture was washed with water. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give a mixture of the mesylated and unmesylated compound. The mixture was dissolved into methanol without further purification and the solution was hydrogenated over 20% palladium hydroxide-charcoal (0.1 g) at room temperature at 3 atmosphere for 5 hours. The reaction mixture was filtered through Celite® and washed with methanol. The filtrate and washing were combined and evaporated under reduced pressure. The resulting syrup was dissolved in tetrahydrofuran (6.5 ml) and thereto tetrabutylammonium fluoride (1M solution of tetrahydrofuran, 0.1 ml) was added below 10°C. After stirring at room temperature, the mixture was evaporated under reduced pressure and the residue was purified by column chromatography using a mixed solvent of dichloromethane and methanol (40:1) to give an oil. The oil was treated with 4N hydrogen chloride in ethyl acetate to give a powder of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[3-hydroxy-4-(1-methylethyl)benzyl]-4-[2-[(2S)-2-(methoxymethyl)morpholino]-ethyl]piperazine dihydrochloride (150 mg).

$[\alpha]_D^{26}$: -1.25° (C=0.2, MeOH)

mp: 218-228°C

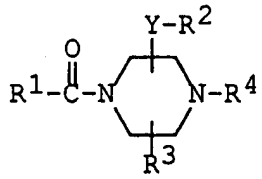
IR (KBr): 3500-3150, 2700-2300, 1644, 1498, 1461, 1282, 1174 cm^{-1}

NMR (DMSO-d_6, δ): 1.00-1.30 (6H m), 2.60-5.10 (26H, m), 6.20-8.20 (6H, m), 9.22 (1H, br s)

MASS (APCI): 632 $(M+H)^+$ (free)

C L A I M S

1. A compound of the formula :



wherein

Y is bond or lower alkylene,

R^1 is aryl which is substituted with 1 to 3 same or different substituent(s) selected from the group consisting of halogen, lower alkyl, lower alkoxy, mono(or di or tri)halo(lower)alkyl, nitro, amino, lower alkylamino, di(lower)alkylamino, lower alkylthio, lower alkylsulfonyl, cyclo(lower)alkylsulfonyl, aminosulfonyl, lower alkylaminosulfonyl, di(lower)alkylaminosulfonyl, pyrrolidinylsulfonyl, morpholinylsulfonyl, pyrrolylsulfonyl, pyridylsulfonyl, pyrrolyl and pyridyl;

R^2 is aryl which is substituted with 1 to 3 same or different substituent(s) selected from the group consisting of lower alkyl, mono(or di or tri)halo(lower)alkyl, mono(or di or tri)halo(lower)alkylsulfonyloxy, halogen, lower alkylenedioxy, lower alkoxy, lower alkoxycarbonyl, lower alkoxy(lower)alkoxy(lower)alkoxy, hydroxy, diphenyl(lower)alkylsilyloxy, tri(lower)alkylsilyloxy, hydroxy(lower)alkyl, cyano, amino, [mono(or di or tri)halo(lower)alkylcarbonyl]amino, lower alkylamino, N-(lower alkyl)-[mono(or di or

tri)halo(lower)alkylcarbonyl]amino, pyrrolidinyl and morpholinyl which may be substituted with lower alkoxy(lower)alkyl or lower alkyl;

R^3 is hydrogen or lower alkyl; and

R^4 is (3-pyridyl)methyl;

(3-pyridyl)ethyl;

3-(3-pyridyl)propyl;

3-(3-pyridyl)propenyl;

3-(3-pyridyl)propynyl;

thiazolyl(lower)alkyl, 1,2,4-thiadiazolyl(lower)alkyl or 1,2,4-oxadiazolyl(lower)alkyl, each of which is substituted with halogen, amino, lower alkylamino or di(lower)alkylamino;

pyrazolylmethyl which may be substituted with triphenyl(lower)alkyl or hydroxy(lower)alkyl;

pyrazolyl(lower)alkyl which is substituted with lower alkyl,

lower alkoxy(lower)alkylmorpholinyl(lower)alkyl or lower alkoxy(lower)alkylmorpholinylcarbonyl-(lower)alkyl;

pyrrolidinyl(lower)alkyl which is substituted with 1 or 2 same or different substituent(s) selected from the group consisiting of hydroxy, hydroxy(lower)alkyl, lower alkoxy and lower alkoxy(lower)alkyl;

piperidylmethyl;

piperidyl(lower)alkyl which is substituted with 1 or 2 same or different substituent(s) selected from the group consisting of halogen, lower alkyl and lower alkoxy(lower)alkyl;

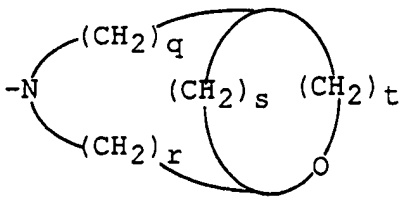
[2,6-di[hydroxy(lower)alkyl]piperidyl](lower)alkyl;

(2,6-dimethylmorpholino)(lower)alkyl;

(2,2-dimethylmorpholino)(lower)alkyl;

(3,3-dimethylmorpholino)(lower)alkyl;

(cis-3,5-dimethylmorpholino)(lower)alkyl;
((3S,5S)-3,5-dimethylmorpholino)(lower)alkyl;
((3S,5R)-3,5-dimethylmorpholino)(lower)alkyl;
(2-methoxymethylmorpholino)(lower)alkyl;
(3-methoxymethylmorpholino)(lower)alkyl;
(2-methoxymethyl-5-methylmorpholino)(lower)alkyl;
(2-methoxymethyl-5,5-dimethylmorpholino)(lower)-alkyl;
(3,5-dimethoxymethylmorpholino)(lower)alkyl;
(2,2-dimethoxymethylmorpholino)(lower)alkyl;
(2,3-dimethoxymethylmorpholino)(lower)alkyl;
(2,6-dimethoxymethylmorpholino)(lower)alkyl;
(2-methoxymethylmorpholino)(lower)alkenyl;
(3,3-dimethylmorpholino)(lower)alkynyl;
(2-methoxymethylmorpholino)(lower)alkynyl;
(2-methoxymethyl-5-methylmorpholino)(lower)alkynyl;
quinoly(lower)alkyl;
[1H-pyrrolo[3,2-b]pyridinyl](lower)alkyl;
[4,5,6,7-tetrahydrothieno[3,2-c]pyridinyl](lower)-alkyl;
[3,4-dihydro-2H-pyrido[3,2-b]-1,4-oxazinyl](lower)-alkyl;
(5,6,7,8-tetrahydro-1,6-naphthyridin-6-yl)(lower)-alkyl; or
lower alkyl which is substituted with a saturated heterocyclic group of the formula :



(wherein
r, s and t are each integer of 1 to 2, and
q is integer of 0 to 2)
which may be substituted with one or two lower alkyl,

provided that when
R^4 is 3-(3-pyridyl)propyl;
3-(3-pyridyl)propenyl;
pyrazolylmethyl which may be substituted with hydroxy(lower)alkyl;
(2-methoxymethylmorpholino)(lower)alkyl;
(3-methoxymethylmorpholino)(lower)alkyl; or
(2-methoxymethylmorpholino)(lower)alkynyl, then
R^2 is not di(lower)alkylphenyl,
and a salt thereof.

2. The compound of claim 1, in which
Y is lower alkylene;
R^1 is phenyl which is substituted with 1 or 2 same or different substituent(s) selected from the group consisting of halogen, lower alkyl, lower alkoxy, mono(or di or tri)halo(lower)alkyl, nitro, amino, lower alkylamino, di(lower)alkylamino, lower alkylthio, lower alkylsulfonyl, cyclo(lower)alkylsulfonyl, aminosulfonyl, lower alkylaminosulfonyl, di(lower)alkylaminosulfonyl, pyrrolidinylsulfonyl, morpholinylsulfonyl, pyrrolylsulfonyl, pyridylsulfonyl, pyrrolyl and pyridyl;
R^2 is phenyl which is substituted with 1 or 2 same or different substituent(s) selected from the group consisting of lower alkyl, mono(or di or tri)halo(lower)alkyl, mono(or di or tri)halo(lower)alkylsulfonyloxy, halogen, lower alkylenedioxy, lower alkoxy, lower alkoxycarbonyl, lower alkoxy(lower)alkoxy(lower)alkoxy, hydroxy, diphenyl(lower)alkylsilyloxy, tri(lower)alkylsilyloxy, hydroxy(lower)alkyl, cyano, amino, [mono(or di or tri)halo(lower)alkylcarbonyl]amino, lower

alkylamino, N-(lower alkyl)-[mono(or di or tri)halo(lower)alkylcarbonyl]amino, pyrrolidinyl and morpholinyl which may be substituted with lower alkoxy(lower)alkyl or lower alkyl;

R^3 is hydrogen; and

R^4 is 3-(3-pyridyl)propyl;
3-(3-pyridyl)propynyl;
(2,6-dimethylmorpholino)(lower)alkyl;
(3,3-dimethylmorpholino)(lower)alkyl;
(cis-3,5-dimethylmorpholino)(lower)alkyl;
((3S,5S)-3,5-dimethylmorpholino)(lower)alkyl;
((3S,5R)-3,5-dimethylmorpholino)(lower)alkyl;
(2-methoxymethylmorpholino)(lower)alkyl;
(3-methoxymethylmorpholino)(lower)alkyl;
(2-methoxymethyl-5-methylmorpholino)(lower)alkyl;
(2-methoxymethyl-5,5-dimethylmorpholino)(lower)-alkyl;
(3,5-dimethoxymethylmorpholino)(lower)alkyl;
(2,3-dimethoxymethylmorpholino)(lower)alkyl; or
(2-methoxymethylmorpholino)(lower)alkenyl,

provided that when

R^4 is 3-(3-pyridyl)propyl;
(2-methoxymethylmorpholino)(lower)alkyl; or
(3-methoxymethylmorpholino)(lower)alkyl, then

R^2 is not di(lower)alkylphenyl.

3. The compound of claim 2, in which

Y is C_1-C_4 alkylene;

R^1 is bis[mono(or di or tri)halo(C_1-C_4)alkyl]phenyl;

R^2 is phenyl which is substituted with 1 or 2 same or different substituent(s) selected from the group consisting of C_1-C_4 alkyl, mono(or di or tri)halo(C_1-C_4)alkyl, halogen, C_1-C_4 alkoxy and hydroxy;

R^3 is hydrogen; and

R^4 is 3-(3-pyridyl)propyl;
3-(3-pyridyl)propynyl;
(2,6-dimethylmorpholino)(C_1-C_4)alkyl;
(2-methoxymethylmorpholino)(C_1-C_4)alkyl;
(3-methoxymethylmorpholino)(C_1-C_4)alkyl; or
(2-methoxymethyl-5-methylmorpholino)(C_1-C_4)alkyl,
provided that when
R^4 is 3-(3-pyridyl)propyl;
(2-methoxymethylmorpholino)(C_1-C_4)alkyl; or
(3-methoxymethylmorpholino)(C_1-C_4)alkyl, then
R^2 is not di(C_1-C_4)alkylphenyl.

4. A compound of claim 3, which is selected from the group consisting of

(1) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)-4-[2-[(3R)-3-(methoxymethyl)morpholino]-ethyl]piperazine,

(2) 1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-(cis-2,6-dimethylmorpholino)ethyl]-2-(3-hydroxy-4-methylbenzyl)piperazine,

(3) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)-4-[2-[(2S,5S)-2-methoxymethyl-5-methylmorpholino]ethyl]piperazine,

(4) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)-4-[3-(3-pyridyl)-2-propynyl]piperazine,

(5) 1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]-2-(3-hydroxy-4-methylbenzyl)piperazine,

(6) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[2-[(2S)-2-(methoxymethyl)morpholino]ethyl]-2-(3-hydroxy-4-methylbenzyl)piperazine,

(7) 1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(3-hydroxy-4-methylbenzyl)-4-[3-(3-pyridyl)propyl]piperazine,

(8) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-chloro-3-hydroxybenzyl)-4-[2-[(2S)-2-(methoxymethyl)morpholino]-

ethyl]piperazine,

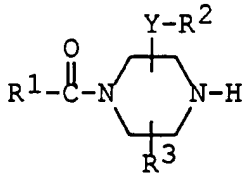
(9) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(4-fluoro-3-methoxybenzyl)-4-[2-[(2S)-2-(methoxymethyl)morpholino]-ethyl]piperazine, and

(10) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[4-(trifluoromethyl)benzyl]-4-[2-[(2S)-2-(methoxymethyl)-morpholino]ethyl]piperazine,

or a pharmaceutically acceptable salt thereof.

5. A process for the preparation of the compound of claim 1 or a salt thereof, which comprises,

(1) reacting a compound of the formula (II) :



(II)

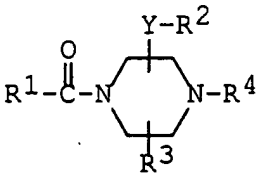
wherein R^1, R^2, R^3 and Y are each as defined in claim 1, or a salt thereof, with a compound of the formula (III) :

$$W_1\text{-}R^4 \qquad \text{(III)}$$

wherein R^4 is as defined in claim 1 and

W_1 is a leaving group,

or a salt thereof to give a compound of the formula (I) :



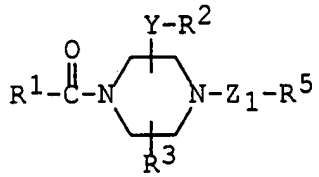
(I)

wherein R^1, R^2, R^3, R^4 and Y are each as defined in

claim 1,

or a salt thereof, or

(2) subjecting a compound of the formula (Ia) :



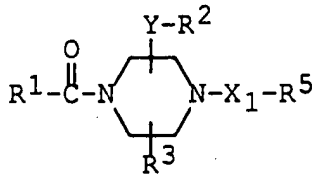
(Ia)

wherein R^1, R^2, R^3 and Y are each as defined above,

R^5 is 3-pyridyl, and

Z_1 is lower alkynylene,

or a salt thereof to a reduction reaction to give a compound of the formula (Ib) :



(Ib)

wherein R^1, R^2, R^3, Y and R^5 are each as defined above, and

X_1 is lower alkylene,

or a salt thereof.

6. A pharmaceutical composition which comprises, as an active ingredient, a compound of calim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

7. A compound of calim 1 for use as a medicament.

8. A method for treating or preventing Tachykinin-mediated diseases which comprises administering an effective

amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof to human being or animals.

9. A compound of claim 1 for use as Tachykinin antagonist.

10. Use of a compound of claim 1 for manufacture of a medicament for treating or preventing Tachykinin-mediated diseases.

INTERNATIONAL SEARCH REPORT

Inte ›nal Application No
PCT/JP 99/06943

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D413/06 C07D401/06 C07D403/06 C07D471/04 C07D413/14
C07D495/04 C07F7/18 A61K31/535 A61K31/495 A61P29/00
A61P3/00 A61P27/02 //(C07D413/06,265:00,241:00),

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 98 57954 A (NAKAI KAZUO ;TAKE KAZUHIKO (JP); AZAMI HIDENORI (JP); EIKYU YOSHIT) 23 December 1998 (1998-12-23) claims 1-4,6,7,9,10; examples 6,15,16,25	1-3,6,7, 9,10
X	WO 97 22597 A (FUJISAWA PHARMACEUTICAL CO ;MATSUO MASAAKI (JP); MANABE TAKASHI (J) 26 June 1997 (1997-06-26) claims 1-8,10,11,14; examples 24,36,51	1-3,6,7, 9,10
X	WO 97 08166 A (SCHERING CORP) 6 March 1997 (1997-03-06) claims 1-3,5,12-14	1-3,9,10
A	EP 0 655 442 A (FUJISAWA PHARMACEUTICAL CO) 31 May 1995 (1995-05-31) claims 1-3,6-8; table 1	1-3,9,10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 May 2000	12/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Goss, I

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/JP 99/06943

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 (C07D401/06,241:00,213:00),(C07D403/06,241:00,231:00), (C07D413/14,265:00,241:00,207:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 May 2000	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Goss, I

2

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

information on patent family members

Inte onal Application No
PCT/JP 99/06943

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9857954 A	23-12-1998	AU	7675098 A	04-01-1999
		EP	0993457 A	19-04-2000
		ZA	9805255 A	06-01-1999
WO 9722597 A	26-06-1997	AU	714931 B	13-01-2000
		AU	1110697 A	14-07-1997
		CA	2240835 A	26-06-1997
		CN	1209125 A	24-02-1999
		EP	0873320 A	28-10-1998
		HU	9901037 A	28-07-1999
WO 9708166 A	06-03-1997	US	5795894 A	18-08-1998
		AU	705683 B	27-05-1999
		AU	5714196 A	21-11-1996
		AU	708834 B	12-08-1999
		AU	6997996 A	19-03-1997
		BR	9608245 A	04-05-1999
		BR	9610277 A	06-07-1999
		CA	2218887 A	07-11-1996
		CA	2228370 A	06-03-1997
		CN	1200120 A	25-11-1998
		CZ	9800228 A	15-07-1998
		CZ	9703423 A	18-03-1998
		EP	0850236 A	01-07-1998
		HU	9801382 A	28-06-1999
		HU	9802552 A	28-10-1999
		JP	10511105 T	27-10-1998
		JP	11504921 T	11-05-1999
		NO	975028 A	30-12-1997
		NO	980848 A	30-04-1998
		NZ	307716 A	28-10-1999
		NZ	318493 A	28-10-1999
		PL	323235 A	16-03-1998
		PL	325339 A	20-07-1998
		SK	27498 A	02-12-1998
		SK	147297 A	08-07-1998
		WO	9634864 A	07-11-1996
		US	5981520 A	09-11-1999
		US	5892039 A	06-04-1999
		EP	0823906 A	18-02-1998
		US	5869488 A	09-02-1999
EP 0655442 A	31-05-1995	AU	689504 B	02-04-1998
		AU	7911194 A	08-06-1995
		CA	2136712 A	30-05-1995
		CN	1107149 A,B	23-08-1995
		HU	71348 A	28-11-1995
		IL	111730 A	06-12-1998
		JP	7242641 A	19-09-1995
		US	5670505 A	23-09-1997
		US	5883098 A	16-03-1999
		ZA	9409228 A	01-08-1995
		BR	9500539 A	31-10-1995